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A CLINICOPATHOLOGIC INVESTIGATION OF THE CAUSES OF MENOMETRORRHAGIA

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NOTWITHSTANDING the tremendous advances made in our knowledge of the activities of the female genital tract, the fundamental causes of either normal or abnormal bleeding are still not fully understood. With the advent of fashionable organotherapy into the therapeutic armamentarium of the gynecologist, a voluminous literature has accrued, tending to make the evaluation of the innumerable forms of therapy impossible. A perusal of the literature on the subject of "abnormal uterine bleeding" or "functional uterine bleeding" reveals that most articles consist of three parts, i.e., the reiteration of accepted facts, the brief recapitulation of the history of the subject, and a prolix discussion of the therapeutic values of the discussed agent. The second perusal of the literature discloses the alacrity with which many authors can get on and get off of the endocrinal bandwagon, with no evidence that they have profited by their enthusiastic errors of judgment. Inconsistency of interpretation of the clinicopathologic picture superimposed on an ever increasing trend to group all forms of menstrual aberrations as endocrinopathic manifestations is so prevalent as to confute even the established facts. Though disturbances of menstruation are symptoms of the variations in the ovarian-uterine relationship rather than entities, and it is the fashion of many to consider these variations as glandular in origin, nonglandular factors do play a major role and must not be overlooked. The widely used and abused term "functional bleeding" is limited to those cases in which, following a

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thorough investigative study, no gross pathologic changes are revealed as possible precipitating factors. To restrict this widely used term within such narrow limits means the probable overlapping of factors, for the separation of an anatomic lesion from a functional disorder, is not possible in every case. While the uterus is the final source of the bleeding and the ovaries directly control the function of the uterus, it is required that the thorough examination include the entire body, the environment, the habits, and complete laboratory investigations. Bleeding due to myomas, polyps, pelvic inflammatory disease, or gestational states obviously is not functional in type. Nor can demonstrable constitutional affections, such as anemia, cardiac diseases, nutritional upsets, and other general disorders that are frequently associated with abnormal bleeding from the uterus, be interpreted as functional.

In this review we offer no new classification, as the present nomenclature is too firmly imbedded in the medical indices. The second reason for not submitting a new system of classification is that we feel the present tendency of each investigator to apply his own terminology has done much to becloud the minds of the medical profession. The third reason is the inadvisability of applying inadequate terms to conditions and changes not fully understood.

Impressed by the marked frequency with which the diagnosis of functional bleeding is made in the presence of demonstrable gross pathology, we have collected a series of cases in which the primary complaint was "abnormal uterine bleeding." The series is large enough to permit conclusions, without recourse to other works. Our interpretations are based entirely on our clinicopathologic findings, and the human element must be considered in this report. The complaint of abnormal bleeding is probably the most frequent symptom which the gynecologist is called upon to treat. The treatment of this symptom without an honest attempt to determine the cause, and resorting to the use of therapeutic agents because of their glamour appeal to the patient and the doctor, has led us to accept the term "buttockal syndrome," which includes those patients who receive their routine injections of minerals, drugs, and hormones "per gluteum" without rhyme or reason. Fortunately the potency of most of the accepted agents is so low as not to constitute a potential danger to the future welfare of the patient. Certainly the prolonged course of therapy is not only a drain on the financial status of the patient, but will in time undermine the patient-doctor relationship.

Because of the frequency of endocrinopathies in early adolescence and during the climacteric, our cases have been limited to those patients in the third and fourth decades of life. The complaint of pain, the fear of cancer, or the admission of possible pregnancy has removed the patient from this series. Though some hold that certain constitutional types are prone to menstrual aberrations, we have found no evidence in our series to support this; a more correct deduction would probably have been obtained if the investigators had delved more deeply into the patient's history and habits. To speculate concerning the unknown is usually entertaining but certainly profitless to the clinician; expensive

and frequently filled with dangerous consequences to the patient. The indiscriminate use of various advocated drugs, hormones, vitamins, and mechanical procedures is an indication of either the gullability of the clinician, the improper interpretation of the clinical findings, or actual ignorance. It is only proper at this point to add that I have been guilty of all three points on many occasions, therefore the casting of stones is performed by hands not entirely unstained.

The diagnosis of abnormal bleeding cannot always be made by any combination of history taking, physical examination, or the ordinary laboratory tests. A study of the endometrium is a valuable adjunct without which the diagnosis is often inaccurate and the resultant therapy empirical. Though hormonal studies are often helpful and even indicated in a few instances, the quantitative determinations reveal nothing of the qualitative activities of the hormones or the ability of the various organs to assimilate them. Bleeding may and does occur from any type of endometrium, and though the endometrial biopsy will indicate the type of endometrium, it does not always form a safe basis for the prediction of the cause of bleeding. Nor do the changes in the endometrial patterns permit a separation of primary or secondary ovarian involvement, thus the true value of the biopsy is its negative information.

TABLE I. MAJOR FACTORS INTERPRETED AS THE CAUSES OF ABNORMAL BLEEDING IN 1,500 WOMEN BETWEEN THE AGES OF 20 AND 40 YEARS, WITH THE PRIMARY COMPLAINT OF ABNORMAL UTERINE BLEEDING

Group A includes those cases in which either the specimen removed at surgery was obtained or the major factor was visualized or outlined by examination. Group B includes those cases in which the diagnosis was made with the aid of endometrial and/or cervical tissue.

THE MAJOR FACTORS	NUMBERS	PER CENT OF GROUP	PER CENT OF SERIES
Group A:			
Causes of bleeding unknown	197	27.0	13.1
Cervix, benign lesions	148	20.2	9.8
Myomata uteri	108	14.8	7.0
Ovary	76	10.4	5.0
Pelvic inflammatory disease	76	10.4	5.0
Cervix, malignant changes	57	7.8	3.8
Tubal gestation	27	3.7	1.8
Senile vaginitis	17	2.3	1.1
Endometriosis interna	16	2.2	1.1
Urethra	4	0.54	0.26
Rectum	3	0.4	0.2
Total	729		
Group B:			
Follicular phase	187	24.0	12.4
No changes; possible functional	124	16.0	8.2
Public	103	13.4	6.8
Endometrial polyp	102	13.2	6.8
Incomplete menstruation	82	10.6	5.4
Endometrial hypertrophy	70	9.1	4.6
Postabortal	53	6.9	3.5
Intermenstrual bleeding	33	4.3	2.2
General group	8	1.0	0.53
Postradiation	5	0.6	0.32
Tuberculosis	2	0.3	0.13
Abnormal gestation	2	0.3	0.13
Total	771		

In Table I we have listed 1,500 cases, for which we have complete clinicopathologic data; no hormonal studies have been included. I have personally studied these cases. For convenience, we group our cases of bleeding into three major groups: (1) Those associated with the gestational states, (2) those with anatomic or functional diseases of the genital tract, and (3) those due to associated causes. In Fig. 1, the major causes are diagrammatically presented. In studies of this type it is difficult to determine the exact border between normal variations and actual pathology, but an honest attempt has been made to present, without bias, the purely clinicopathologic evidence. There is an overlapping of factors, for a large myoma must influence the ovarian and endometrial relationship; thus the possibility of coincidental occurrence must be considered. Most of these cases were treated as "functional

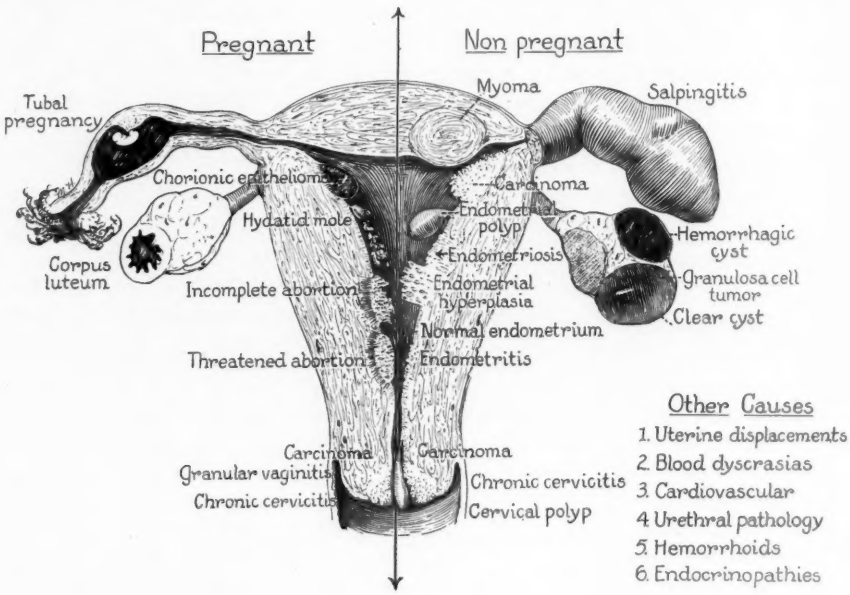

Fig. 1.

bleeding" prior to the final diagnosis, and the frequency of this misinterpretation will be emphasized in certain of the major classifications. For convenience of presentation, the series has been divided into two groups: first, those in which the actual specimen removed at surgery was studied or in which the diagnosis was made by visualization or palpation of the causative factors, and second, those cases in which the diagnosis was made with the assistance of endometrial and (or) cervical tissue examination.

CAUSE OF BLEEDING UNKNOWN

In 197 (13.1 per cent) instances, a careful study of the clinical history and removed corpus uteri offered no clue as to the cause of the patient's complaint of abnormal bleeding. In 84 of these cases we have sufficient ovarian tissue for histologic study and in all instances, evidence of

normal cellular function is present. From a study of these cases postoperatively, it is our impression that hysterectomy in the presence of normal ovarian tissue is not followed by signs or symptoms of ovarian degeneration, though it does appear probable that some modification of the ovarian action may occur.

What is the microscopic appearance of normal ovarian function? Our interpretation is purely cellular and takes no notice of possible and even probable upsets of the ratio-relation between the various follicular responses and the effects such disruptions may have upon the uterus, the pituitary, and other glands of the body. There has been no constant relation between the presence of cystic ripening follicles and the endometrial patterns so far as the complete follicular cycle can be demonstrated. Normal appearing follicular elements with evidence of corpus luteum formation presupposing ovulation are accepted as the norm. But we do find normal appearing endometrium, myometrium, and ovaries in patients with clinical evidence of abnormal uterine bleeding. Selective staining of the vascular channels and the ratio of the myometrial elements has offered no clue to possible causative factors. Too many of the ovaries removed at the time of hysterectomy contain normal appearing corpora hemorrhagica, misinterpreted both clinically and pathologically as "chocolate cysts of Sampson." Ovaries with thin-walled cysts are removed and their importance as causative factors in abnormal bleeding is open to doubt, as many of them are nothing more than evidence of augmented ovarian activity. The endometrial pattern is correlated with the menstrual history, and though the fallacy of this is appreciated, the conclusions in this group are dependable from a clinical point of view. An attempt to link the presence of corpus luteum cysts as major factors in abnormal bleeding, especially when the endometrium is of the secretory type, is not conclusive. However, cysts of this type do apparently serve as a factor in some of the cases. To illustrate the discrepancy of endometrial response, we do find the follicular pattern as well as the luteal pattern in the endometrium associated with corpus luteum cysts. Thus another stumbling block to any theory of interrelationship is presented, and the value of the endometrial biopsy correlated with the pelvic findings is not absolute in its interpretation. Why these cases bleed and how to treat them are some of the bugbears of the investigative gynecologist. Fortunately most of the patients falling into this group, will, in spite of conservative therapy, recover spontaneously. It is highly probable that the glandular system can be disarranged temporarily, thus the admonition that so-called "functional" bleeding cases be treated conservatively as long as possible, hoping that the disrupted system will rearrange itself and a spontaneous recovery result. It is our opinion that many of the "cures" of the exploited agents frequently exposed as inert, would have recovered regardless of the medication employed.

One hundred and twenty-three of the 197 patients received endocrinal therapy in various forms, frequently supported with minerals and vitamins. A review of many of the therapeutic charts offers no logical

reason for their use. Some clinicians have a routine schedule of injections, usually beginning with the estrogenic substances, then changing after a specified number of injections have been given. This is unfortunate, especially in large clinics, as the patient is frequently lost sight of and the injections continue over a period of years, the patient enjoying a probable psychic uplift from the injections and in time forgetting why she received the first treatment. The results of this varied form of therapy cannot be evaluated. Too frequently patients without demonstrable abnormalities return to normal, so far as bleeding is concerned, before the investigation is completed and proper therapy can be instituted. Thus, what constitutes proper therapy is questionable. A low hemoglobin can directly precede as well as follow menometrorrhagia, and it is extremely important to always bear in mind that the individual threshold of anemia, as a factor, varies considerably. A more complete preoperative study of the patients in this group and a knowledge of the limitations of various therapies along with an appreciation of the importance of constitutional disorders, may have prevented the indications for surgery in many instances.

THE CERVIX

In 148 (9.8 per cent) patients, the cervix was considered the source of the abnormal bleeding. Endometrial studies were made in 71 of these cases and 39 showed definite inflammatory reaction of the endometrium removed from the lower uterine cavity. This is consistent with our punch biopsy studies of the endometrium in the presence of chronic endocervicitis. The majority of these cases showed an actual extension of the inflammatory process into the lower portion of the uterus. That such an inflammatory process can serve as a causative factor is accepted, though frequently overlooked. In 91 cervices, polyps arising from various levels of the cervical canal were demonstrated. Bleeding in the presence of a polyp is usually metrorrhagic in type and varies markedly in amount. However, it is not uncommon to find even large polyps in the absence of menstrual aberrations. Apparently some other factor besides the actual presence of a foreign body may serve as the instigator to the abnormal bleeding in this group. Examination of the endometrium in the presence of cervical polyps has shed no light on the cause from this standpoint. The so-called "erosion" of the portio vaginalis of the cervix must also be considered, though the bleeding is usually very scant and tends to follow trauma.

The management of cervical lesions is threefold in type: (1) The interpretation of the pathologic changes by careful visualization of the cervix with properly taken biopsies, when doubtful areas are noted. We place little credence in either the iodine test or the colposcope, except for the psychologic effect which such procedures seem to have on the patient. Adequate exposure and good light seem sufficient. We feel that there is a tendency on the part of many to place too much dependence on the iodine test, and we have practically discarded it from our clinical armamentarium. To use the colposcope properly requires a thorough knowledge of the cervix, as visualized under magnification, a knowledge

few of us have even without magnification. To acquire a working ability with this instrument predicates careful correlation between the visual pattern and the histologic findings in hundreds of cases. We feel that this instrument does have possibilities, but to advise its routine use by the practicing gynecologist, as a dependable adjunct in the ruling out of early malignant changes of the cervix, does not seem warranted. Our routine study of the cervix consists of adequately exposing the cervix, a strong light, careful cleaning of the cervix to remove foreign substance, palpation of the portio vaginalis preferably with the ungloved finger, and the excision of suspicious areas for microscopic study. (2) Adequate dilatation and study of the cervical canal to rule out polyps, canal abscesses and strictures, and endocervical malignancies. (3) Proper selection of either the cautery or one of the various surgical procedures.

The delicate application of the nasal tipped cautery to cervical gland cysts is only of cosmetic value, and when repeated at frequent intervals, may serve as a factor in producing strictures of the external os. If cauterization is indicated, it should be thorough. Local heat, either in the form of douches or by one of the many mechanical apparatus, is frequently of value before actual cautery or surgery, especially in the presence of marked infection and tissue edema. No cervical manipulation should be undertaken in the presence of an acute infection of the cervix or with demonstrable extension of the inflammatory process into the parametrial regions. We have stressed the importance of palpating the uterosacral ligaments, and the presence or absence of induration of these ligaments guides our therapeutic procedure. In this series, 4 women complained of severe lower abdominal pains following cauterization, and on examination were found to have either a flare-up of a previous pelvic inflammatory disease or an extension of the cervical inflammatory process into the parametria; 2 patients developed pelvic abscesses and 5 patients presented with abscesses of the cervical canal. Though not included in this series, we have post-mortem evidence of two patients who, following deep cauterization of acutely infected cervices, developed streptococcal peritonitis and multiple abscesses scattered throughout the body.

Of the 91 polyps studied, malignant changes were demonstrated in one instance. A tissue review of 400 cervical polyps revealed 7 malignancies; this does not include those patients found to have fundal malignancies, associated with the incidental polyp. This is not a true index of the percentage of malignant polyps, as it is not an exaggeration to assume that approximately 25 per cent of the polyps removed are not subjected to microscopic study. A probable figure would be that 2 per cent of the polyps arising in the cervix will show malignant changes. The oft repeated statement that cervical polyps are found more frequently in women who have borne children is not consistent with our findings. Of 183 women with cervical polyps, 39 (21 per cent) women had never been pregnant; thus statistically speaking, polyps are nearly twice as frequent in women who have never borne children. In spite of the apparent low incidence of malignancy, every polyp should be subjected to microscopic study.

Myomas.—The relative infrequency of myomas as a possible cause of abnormal uterine bleeding is explained in our selection of the cases for this series. In the 108 (7 per cent) women with demonstrable myoma, the majority of the myomas were intramural in location. We have been impressed with the frequency of endometrial polyps occurring in the presence of myomas as a possible factor in the oft repeated statement that the endometrial pattern is of the endometrial hyperplasia type. A similar disorderly endometrial pattern is frequently present because of the pressure of the encroaching tumor on the endometrial layers. Dilated glands, dense stroma, and other changes consistent with the frequently accepted picture of endometrial hyperplasia lead to a misinterpretation of the causes of bleeding. This misinterpretation also accounts for the statistical studies showing an increase in the number of endometrial hyperplastic reactions as an indication of myoma-ovarian dysfunction factors in the origin of myoma. There is no demonstrable distinction in the symptomatology or in the pathologic picture of the myomatous and the nonmyomatous uterus. The subserous nodules have little effect on the uterine musculature while the nodule located in the submucosal position is often associated with diffuse hyperplasia of the uterine wall; a subsequent involvement is then frequently found in the neighboring endometrium. The intramural tumors are found with and without demonstrable hyperplasia of the surrounding tissue and the size of the tumor mass does not always predict the presence of these changes. Thirty-eight uteri showed no demonstrable changes in either the endometrium or the myometrium, except for the actual myomatous nodules, yet some of these cases with minimal tissue changes gave evidence of profuse and prolonged hemorrhage. Histologic studies of ovarian tissue in the presence of large myomas in 28 instances showed definite thickening of the tunica albuginea in 21 instances, sufficient to interfere with normal ovarian function. However, we do find large myomas in the absence of abnormal bleeding, showing normal endometrium and normal ovaries with corpora lutea. Thus, the presence of large tumor masses does not necessarily predicate abnormal ovaries. This mechanical impediment to normal ovarian activity may serve as one of the factors of abnormal bleeding; it may also be assumed on the basis of histologic study and the correlation of the clinical findings, that the menopausal symptoms, frequently the sequelae to hysterectomy for myomas, are not necessarily dependent on either the removal of the uterus or the mechanical interference of the ovarian blood supply. Our investigation does not support the frequent contention that endometrial hyperplasia, supposedly an indication of hyperestrinism, is a common occurrence in myomatous uteri. If our tissue studies have been correctly interpreted, there seems to be a definite ovarian dysfunction rather than a hyperfunction. It must be appreciated in this type of study that the presence of a myoma has classified the case as bleeding of an organic origin rather than of a possible so-called functional etiology.

Though not necessarily concerned with this study, careful examination of the round ligaments was carried out in every instance, and we

cannot ascribe to the statement that there is an associated hypertrophy of these ligaments in the presence of myomas. We do see definite enlargement of the round ligaments, but we also see definite atrophic changes.

THE OVARY

The most difficult group for classification are those cases in which the ovary is designated the precipitating factor, for even in the presence of large tumors, with a very small amount of demonstrable functioning ovarian tissue, normal function may be maintained. Frequently the bleeding may be the result of hyperemia secondary to the large pelvic mass. Histologic studies of grossly normal ovaries in the presence of symptomatic retroposition of the uterus, myomas, or chronic inflammatory lesions of the pelvis will often disclose a definite increase in the fibrous tissue with an associated decrease in the epithelial elements of the ovary. That such an increase of inactive elements in the ovary predicates a decrease in the normal function of the gland is a logical deduction. However, what degree of upset in the fibrous-epithelial tissue ratio determines a derangement of function must vary with the individual; here again enters that so-called refractive index of ovarian-uterine relationship. This inability to determine the passing of the ovarian tissue pattern from the normal state to that of a pathologic state adds to the difficulty of indexing the ovary as a factor in the cause of abnormal uterine bleeding. However, abnormal changes in the ovaries of 76 patients (5 per cent) were accredited as being the cause of this disorder. In reviewing more closely the clinical manifestations of this group, we could find no typical bleeding pattern peculiar to ovarian pathology. There were 7 malignancies of the ovary, and of these, 5 had received various forms of endocrine therapy. Granulosa cell tumors were present in two instances and one of these patients had received large amounts of estrogenic substance over a period of five months prior to surgery. Hemorrhagic cysts and other types of cysts arising from the follicular apparatus accounted for the remainder. The absence of dermoid cysts, fibroma, and endometrial cysts is explained by the fact that they are usually associated with pain as the outstanding complaint.

Regardless of the increasingly voluminous reports on the importance of the uterus in relation to normal ovarian function, we feel that if the tissue study of the ovary at the time of hysterectomy reveals normal functioning follicular elements, the function will continue as normal after the removal of the uterus. We base this conclusion on the clinical findings of these patients following surgery. It must be admitted that the proper procedure would be to re-examine the ovaries several years following the first examination, but this is a difficult thing to do. We do not think that experimental studies in lower animals can be transposed to include women, so far as this reaction is concerned. By carefully studying the ovaries it is possible to predict whether or not the patient will develop menopausal symptoms following surgery. It must be stressed that what constitutes clinical evidence of ovarian dysfunction is not too dependable from a statistical approach.

PELVIC INFLAMMATORY DISEASE

No attempt is made to separate the postabortal type of pelvic inflammatory lesion from the specific form. Of the 76 (5 per cent) cases presenting in this group, the bleeding probably results from disturbances to the ovary, sufficient to interfere with its regulation of menstruation. A second possible factor is the direct extension of the inflammatory process into the myometrium, thus preventing normal endometrial changes by disturbing the uterine vascular bed. The ovarian changes are usually mechanical, the capsule being thickened secondarily to the inflammatory process and thus preventing ovulation. It must be understood that the ovary does possess remarkable powers of rehabilitation, and all forms of conservative therapy should be utilized before resorting to surgery. As stated above, biopsy studies of the ovary at the time of pelvic surgery frequently permit prediction of the probable time of onset for menopausal symptoms. However, in many instances, leaving these grossly normal but physiologically impotent ovaries is of psychic rather than glandular importance. We have been unable to demonstrate any harm in leaving these physiologically inactive ovaries following surgery, and it does salve both the surgeon and patient. The probability of such handicapped ovaries forming large cysts and thus requiring further surgical intervention is possible, and though this has long been an argument in favor of removing both ovaries, our studies do not support this argument. It is true that immediately following any type of pelvic surgery, one or both ovaries may become markedly enlarged. The majority of these enlarged ovaries will return to normal size in from two to three months without any form of therapy. The cause of this enlargement, even in the absence of actual trauma to the ovary or the tissue in its immediate vicinity, is not known. It is shown that hysterectomy following a previous bilateral salpingectomy is 8 times more frequent than oophorectomy following a previous hysterectomy and (or) salpingectomy. We have noted no evidence to support the statement that the removal of one ovary will alter the future activity of the remaining ovary, assuming of course that the remaining ovary is normal at the time of surgery. One of our patients whose right tube and ovary were removed along with the appendix at the age of 9 years, had three normal pregnancies and finally presented with a large symptomatic myoma. Biopsy studies of the remaining ovary showed normal functioning tissue. We have been impressed by the frequency with which the right tube and ovary are removed in the presence of appendiceal lesions, the operative diagnosis usually being cysts of the ovary or chronic inflammatory changes. Tissue studies usually reveal a low grade perisalpingitis. Both tube and ovary, if left intact, will return to normal within a very short period of time following the removal of the inflamed appendix. The use of the McBurney incision protects the left tube and ovary.

CARCINOMA OF THE CERVIX

Fifty-seven (3.8 per cent) women complained of irregular bleeding or spotting without either pain or the admitted knowledge of a pelvic

mass. No early (Stage I) cases were found, and the youngest patient was 23 years of age; this patient received hormonal therapy for a period of eleven months prior to her first pelvic examination and finally came to the clinic because she was not satisfied with the type of treatment she was receiving. Twenty-three patients in this series received various forms of hormonal therapy; only 19 of the 57 patients gave a history of having had a pelvic examination before admission to the clinic. Of the 57 patients, studies of the endometrium were carried out in 41 cases, and of this group 2 showed changes suggesting endometrial hyperplasia. Subsequent biopsy studies of the endometrium were impossible because of the early institution of therapy. In two instances carcinoma of the fundus was found on curettage. One with the malignancy limited to an endometrial polyp revealed no further malignancy of the endometrium following hysterectomy. This is not a rare incident, though very disquieting to the pathologist who has not been too certain of the primary interpretation of the tissue removed by curettage. The relative paucity of fundal malignancies in this series is explained on the age limitations.

TUBAL GESTATION

Though the diagnosis of ectopic pregnancy, following the rupture with intraperitoneal hemorrhage, is not difficult, the so-called silent tubal pregnancy offers diagnostic problems. In 27 (1.8 per cent) cases, tubal pregnancy was erroneously diagnosed prior to surgery. The complaint was bleeding, and the most frequent diagnosis was pelvic inflammatory disease. In none of these 27 cases was pregnancy suspected. The value of the endometrial biopsy, in the presence of uterine bleeding as a diagnostic adjunct, is dependable if the tissue shows definite decidual changes in the endometrium. That decidualike changes in the endometrium can occur in the absence of pregnancy has been proved, and though the finding of a decidualike reaction is suggestive, the study of the endometrium in this group was of little value.

SENILE VAGINITIS

Of the 17 (1.1 per cent) women with senile vaginitis, 9 had received radium for "benign functional uterine bleeding"; subsequent investigation showed that none had endometrial studies prior to irradiation. Five of the 9 radiated patients received their treatments before the age of 25 years. Three patients had been radiated for "temporary sterility," with subsequent permanent destruction of the ovarian activity, followed by atrophic changes of the vaginal mucosa. The response of this type of vaginitis, to specific hormonal therapy, has been very disheartening in our hands. Pelvic "house cleaning" for extensive endometriosis accounted for the remaining 5 patients. A review of the pathology of one of these cases revealed that the "chocolate cysts of the ovaries" were simple hemorrhagic cysts with ample normal ovarian tissue to warrant excision of the cysts rather than radical extirpation. Patients with infectious or chemical vaginitides complain of discomfort rather than vaginal spotting.

ENDOMETRIOSIS INTERNA

Heterotopic endometrial tissue was found in the myometrium of 16 (1.1 per cent) uteri, removed with the diagnosis of "fibrosis uteri" and because of uncontrollable uterine bleeding. Though this lesion is not a rare entity, menstrual distress rather than abnormal bleeding is the predominant complaint. Adenomyomas were also a frequent occurrence in the myoma group. Bleeding is probably due to a lessened efficiency of uterine musculature, and also secondary to a congestion of the endometrial venous plexus, arising from the interference to the normal vascular bed.

THE URETHRA

Adequate proof that the patient's interpretation of her complaint is of little factual value is well borne out by 4 (0.26 per cent) patients complaining of abnormal bleeding; examination in each instance revealed the urethra as the source of the bleeding.

THE RECTUM

This group should be classed as an oddity. Three (0.2 per cent) patients with suspected uterine bleeding were found to have bleeding hemorrhoids. Of further interest is the history of one patient who had been treated extensively with endocrines; little relief was obtained with this form of conservative therapy.

CASES INTERPRETED WITH THE AID OF ENDOMETRIAL STUDIES

The Follicular Phase.—In 187 (12.4 per cent) patients, a thorough general and pelvic examination revealed no cause for the abnormal bleeding. In the majority of these cases the basal metabolic rate was also studied. Endometrial studies showed histologic patterns, consistent with those changes interpreted as occurring in the follicular or proliferative phase of the menstrual cycle. It is well understood that single punch specimens removed from the fundal portion of the uterine cavity do not always give the true endometrial picture, but this site is the most dependable and consistent in its response. Unfortunately it is in this group that our data do not permit an exact corroboration of the cyclic endometrial changes with the calendar phase of the menstrual cycle. To obtain such data, it is necessary to have dependable records of consecutive menstrual periods, tabulated by the patient at the time of occurrence and not by memory during her visit to the clinic. Hospital records and dispensary notes are of no value. Of the 187 studies, there are 8 endometria interpreted as typical endometrial hyperplasia. It is difficult to determine whether the condition commonly termed endometrial hyperplasia is the same as the one to which Cullen first applied the term, or whether the endometrial changes often discussed are due to hypertrophy, to edema, to which the term endometrial hyperplasia has been loosely applied. This common discrepancy and loose handling of terminology is a serious obstacle to statistical studies. In favor of these 8 cases being true hyperplasia, secondary to hyperestrinism, is the fact that regardless of the various forms of hormonal therapy and repeated

curettage, hysterectomy was finally resorted to in order to control the uterine hemorrhages. The term endometrial hyperplasia has been bandied about with little attempt to apply it properly. In the first place it is a poor descriptive term, for a careful detailed study of the stroma will reveal that there is not an actual hyperplasia of the cellular elements, the increased density being the result of the increased size of the endometrial glands. Second, its persistent misuse in practically all benign derangements of the endometrial patterns has rendered it of little scientific value. Careful review of the many articles and their attended photomicrographs and case reports supposedly of endometrial hyperplasia, amplify the fact that the majority of the cases are not endometrial hyperplasia. Endometrial hyperplasia is that change in the tissue pattern associated with a marked and persistent overproduction of the estrogenic substance, a total absence of ovulation, and a clinical history of profuse uterine hemorrhages interspersed with periods of amenorrhea. The changes associated with persistent failure of ovulation, either the result of mechanical or physiologic impediments to normal ovarian activity, are not endometrial hyperplasia. The entire interpretation is so muddled and poorly understood that a dogmatic classification is impossible, as well as impractical. This ovarian dysfunction, associated with interference of ovulation, causes changes corresponding to the middle follicular or proliferative phase of the menstrual cycle; to apply the term endometrial hyperplasia to all endometria, because of variations in the size of the glands and possible alterations in the density of the stroma, is not consistent with the clinicopathologic investigations. This tendency to misinterpret the histologic picture has brought about confusion in the literature, because many of the therapeutic claims are based on these wrong interpretations.

Monthly endometrial biopsies from accepted normal women over a period of several years reveal that anovulatory periodic bleeding does occur in the absence of either demonstrable anatomical, endocrinal, or constitutional abnormalities. Thus the presence of the follicular type reaction of the endometrium in the late luteal phase of the menstrual cycle does not necessarily indicate either abnormal ovarian action, pathologic changes in the uterus, or permanent upset in the polyglandular relationship. A single biopsy specimen, though valuable, must be interpreted with each case; carefully tabulated menstrual calendars supported by comments on the emotional, constitutional, and physical upsets are a necessary adjunct to correct interpretation of the ovarian-uterine relationship. Thickening of the capsule of the ovary, preventing ovulation, with subsequent corpus luteum formation, in most instances is followed by a persistence, but not an oversecretion, of the follicular substance. Thus the endometrial picture is one suggesting a prolonged but rather sluggish response, instead of a hypersecretion of the estrogenic substance associated with endometrial hyperplasia. The importance of the anterior lobe of the pituitary gland in these cases is appreciated but still speculative. Though gonadotropic therapy will elicit an occasional response suggesting reactivation of the ovaries, the response is all too

frequently only temporary. Studies made on the ovaries of individuals who have received various forms of gonadotropic substance frequently reveal tissue totally impossible of stimulation. Since, however, most patients give a history of having been benefited by the injections, the influence is either on a psychic basis or the injected substance must act directly upon the uterus.

NO CHANGES; POSSIBLE ENDOCRINOPATHIC MANIFESTATIONS

The clinical histories are accurate enough in 124 (8.2 per cent) instances to permit a factual correlation of the endometrial pattern with the patient's menstrual history. The usual complaint is of several profuse periods, following a preceding normal menstrual history. Not infrequently a careful questioning will reveal that the patient has had similar episodes of abnormal bleeding over a period of the past few years. The most satisfactory therapy is symptomatic treatment of the occasional associated low grade anemia. However, low grade anemia is so common among the female patients of a large charity clinic, that its importance as a factor in this group must be open to doubt. The majority of these patients will return to a normal cyclic menstrual life with or without the benefit of any type of treatment. In most of these cases, the endometrial studies have offered no clue as to why the patients are bleeding and the majority of the endometrial patterns are of the luteal type, suggesting normal ovarian activity. Then there is the patient with the definite anemia, complaining of symptoms suggesting general debility, who occasionally gives a history of profuse bleeding, but more frequently complains of periods of amenorrhea.

THE PUBLIC

For want of a better descriptive term, we have used "The Public," to include those 103 (6.8 per cent) patients who, after careful questioning and examination, including endometrial studies, were assured that their menstrual periods were normal. It is this type of patient, susceptible to advice from the medical columns, the advertising brochures, friends, and family, that must be handled with the utmost care. Gathering pathologic evidence supports our impression that the continuous injudicious use of substitutional hormonal therapy, in the presence of normal functioning glands, will produce permanent destructive changes in the ovary. Relying solely upon the patient's unsupported statement that her periods are abnormal predicates, in many instances, improper and possibly dangerous therapy. The correct handling of this group necessitates a careful explanation to the patient that normal periods vary in cyclic appearance, duration of flow, and amount of blood loss. Simple placeboes may be of value in some instances.

ENDOMETRIAL POLYP

The curettings from 102 (6.8 per cent) patients were interpreted as being endometrial polyps; certainly they are more common than usually accepted. The abnormal tissue response with the "Swiss-cheese" pattern leads many an unversed pathologist to diagnose endometrial hyperplasia.

We have also been impressed with the frequency of endometrial polyps in the absence of abnormal bleeding. Here again, other factors than the presence of a foreign body in the uterine cavity must be looked for to account for the bleeding. A thorough study of the removed tissue, with an appreciation of the microscopic changes consistent with the polyp, will clarify the diagnosis. The missed diagnosis of the polyp accounts for the excellent therapeutic results of those cases interpreted as endocrinopathic manifestations.

INCOMPLETE MENSTRUATION

Though this is a relatively new addition to our interpretation of endometrial patterns, we have listed 82 (5.4 per cent) cases in this group. We are uncertain in some instances as to whether or not we are dealing with small polyps or an incomplete menstruation. The actual interpretation of the tissue changes is still unsettled, and we recall listing some of these cases as "peculiar foreign body-like reactions." It is also possible that a small fragment of retained endometrium, with its subsequent interference to normal tissue response, may later develop into a true endometrial polyp. Serial sections of uteri offer support to this possibility, but have not as yet given us sufficient evidence to advance it as a proved fact.

ENDOMETRIAL HYPERTROPHY

Seventy (4.6 per cent) patients were diagnosed as having either a malposition of the uterus, partial descensus of the uterus, or pelvic varicosities, on the basis of changes in the endometrial patterns. An occasional patient with symptomatic uterine malposition, complaining of profuse and prolonged periods, will experience relief from the menstrual aberration following mechanical correction of the malposition. The endometrium, which prior to the correction contained an increased number of blood vessels, and also showed an increase in the number of glands for the calendar date of the menstrual cycle with a definite increase in the density of the stromal cells, will return to an accepted normal pattern within several months following correction. However, if the mechanical interference has been present long enough to bring about permanent changes in the myometrium, the correction of the interference will have no effect on the menstrual aberration. This fact must be appreciated when surgical intervention for correction of the malposition of the uterus is contemplated and also accounts for the all too frequent failure of the surgical procedure. Thus, the so-called hypertrophy is secondary to the hyperemia of the uterus induced by mechanical changes in the vascular bed of both the pelvis and the uterus. The personal factor must also be accepted, as many cases with sufficient demonstrable changes in the pelvic supports to warrant extensive interference with the vascular bed, present no abnormalities whatsoever. With the rapid progress in our knowledge of the endometrial changes, the descriptive terminology should be revamped. However, our knowledge is far from complete, and it is better that we struggle along with the present inapt system than to apply improper terms at the improper

time. We have grouped these various changes with their numerous inexplainable ramifications as endometrial dysplasias, which applies only to an abnormality of form, without implying either the cause or the type of the abnormal changes.

POSTABORTAL

Though the patients in this group strongly denied the possibility of pregnancy, both before and following the curettage, 53 (3.5 per cent) patients had endometrial changes consistent with retained secundines, evidence of previous intrauterine pregnancy. Into this group should be placed some of the so-called "follicular type" of endometrii, for the diagnosis of retained secundines is not always possible after the patient has bled for several days. One is impressed by the frequency with which conception apparently can occur in human beings without the benefit of the male factor. It is of interest that many of these patients had received hormonal therapy; this type of patient rarely gives an honest answer to the physician's questions, and therapy frequently varies so much as to be ludicrous.

INTERMENSTRUAL BLEEDING

Thirty-three (2.2 per cent) women stated that they bled at regular two-week intervals, and as a rule, one period was several times longer than the other period. Eighteen of these patients were married and none of them had ever been pregnant. Explanation to the patient of a probable cause of the sterile marriage was followed by pregnancies in 7 cases. Most of the intermenstrual periods were associated with a sense of discomfort, the discomfort varying conversely with the amount of blood flow. Twenty-one of the patients had undergone surgical procedures; 18 for the removal of the appendix, and three for operations of the ovary. In no instance did the surgical procedure bring relief for the discomfort complained of by the patient prior to the operation. Twenty-six of these patients had received hormonal therapy for this accepted physiologic phenomenon. Why these patients bleed is another unanswered problem in our study of the menstrual phenomenon. Suffice to add that we know of no form of effective therapy.

THE GENERAL GROUP

Into this group we have placed 8 (0.53 per cent) patients, including one with acute lymphoid leucemia whose subsequent postmortem studies revealed almost a solid infiltration of the ovaries and uterus with round cells; I wrongly interpreted the endometrial biopsy as an acute endometritis. Four of the cases were proved cardiac problems, 3 having been treated for the uterine bleeding, with no attention being given the evidence of gross cardiovascular pathology. The menstrual periods became normal in every instance following proper treatment of the cardiac failure. Unfortunately, our experience is limited with this group, as the medical clinics appreciate the relationship of such conditions to abnormal bleeding and treat the bleeding as a minor symptom of the general picture.

POSTRADIATION

Though squamous cell metaplasia of the endometrium is no rarity, its presence is frequently very confusing to both the pathologist and the clinician. Five (0.32 per cent) patients gave a history of radiative castration for benign uterine hemorrhage, and subsequent study of the endometrial changes showed definite benign metaplastic changes. This cellular change is probably the end result of a persistent chronic irritation, but an additional factor must be included to account for its not being a more frequent change in the rapidly increasing number of cases receiving this type of uncontrolled therapy. The routine use of small dosages of x-ray or radium to control bleeding and effect a "temporary amenorrhea" in young women is injudicious because of the wide variability in the individual responses to irradiation. There is also increasing evidence adding more probable hazards to irradiation. It has been definitely shown that defective embryos may be produced after irradiation and may also influence the subsequent generation. Though this evidence has been limited to lower forms of life, it warrants serious consideration before advising routine irradiation in young women. The bleeding in these cases is usually scant, and described as a profuse, foul, blood-streaked discharge. We always suspect malignancy and usually find a partial to complete atresia of the cervical canal. True pyometria has not been included, as this type of case presents with pain and discomfort.

TUBERCULOSIS

Though we have access to a large tubercular clinic, only two instances of endometrial tuberculosis are included in our series. In each instance the preoperative diagnosis was wrong.

ABNORMAL GESTATION

To our incomplete abortions and our ectopic pregnancies, we must add one hydatidiform mole and one chorionepithelioma. The mole was correctly diagnosed by the nurse on duty prior to examination by the attending physician. The chorionepithelioma was apparently limited to the uterus and was also diagnosed correctly preoperatively. Lutein cysts of the ovary were present in both cases and returned to a palpable normal size within a period of three months following surgery.

DISCUSSION

A lengthy discussion is not indicated in this report. We have made no attempt to summarize even the most recent work in this field. We have merely outlined our findings and our interpretations as we have seen them. Our interpretations and our deductions are necessarily influenced by the works of Bartelmez, Cullen, Corner, R. T. Frank, Fluhmann, Hamblen, Hartman, Haigs, Novak, and many others. A brief summary of the group reveals no typical set of symptoms peculiar to specific pathologic changes of either the uterus or the ovaries. The patient with the minimum of demonstrable changes may bleed more profusely than the individual with widespread pathologic changes in the pelvis. Running through the entire picture is the apparent fact that, in

spite of anatomic lesions, other factors must be considered as probable etiologic causes precipitating the abnormal bleeding. We are of the opinion that the surface of this subject is just being scratched, and that not only must the problem be approached from an endocrine angle, but the clinicopathologic aspects must not be forgotten or discarded because of the waves of therapeutic and investigative enthusiasm.

SUMMARY

1. A series of 1,500 women between the ages of 20 and 40 years, complaining primarily of abnormal uterine bleeding, are presented from a clinicopathologic approach.

2. The misinterpretation of the endometrial patterns and the misapplication of terminology have done much to complicate the present status of investigative and therapeutic work in menstrual aberrations.

3. Though endocrinopathic manifestations are important factors in the cause of abnormal uterine bleeding, factors of anatomic nature are more common and should be ruled out before interpreting the cause as functional or dysfunctional in type.

4. Therapy, to be adequate, demands a thorough and complete investigation of the entire system with a proper interpretation and appreciation of the findings.

5. No attempt has been made to offer new theories, change the classification, or advance new ideas of therapy; the clinical aspects of the case and the associated tissue changes have been studied and presented with personal interpretations.

523 WEST SIXTH STREET

THE ROLE OF THE FALLOPIAN TUBES IN THE SPREAD OF PELVIC CANCER

REPORT OF A CASE WITH A BRIEF REVIEW OF THE LITERATURE

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THE question of the transtubal cancer dissemination is of high clinical significance as well as of pathologic interest and has been given a great deal of attention by numerous investigators. In reviewing the literature on this problem, Reichel,[11] in the year 1888 was probably the first to draw attention to the Fallopian tubes as a possible passageway through which cancer cells may travel. He reported two cases of ovarian carcinoma, each associated with a small carcinoma of the uterine mucosa. In his discussion of the presumable origin of the uterine growths in these two cases, he suggested the new idea that they may have arisen from the implantation of cancer cells escaping from the ovarian carcinoma through the lumina of the tubes.

The importance of this subject was at once apparent to the gynecologist and surgeon.

V. Franqué[2] was the next to describe an instance of primary sarcoma of the uterus in which particles of the uterine growth microscopically were found to be

lying free in the lumen of the right tube. Metastases of sarcoma were present on the surface of the right ovary, in the right broad ligament, and in the anterior vaginal wall. From the description given, it seems evident that the tubes have undergone inflammatory changes. The 53-year-old patient had a preliminary curettage two weeks before she was operated upon. Franqué was inclined to regard the transportation of tumor particles from the patent fimbriated end of the Fallopian tube into its free lumen in this case as probable but not definitely proved.

Morinaga[5] reported a second case from v. Franqué's clinic and his description of a primary carcinoma of both the Fallopian tubes with secondary uterine growth is rather remarkable in its completeness and observation.

Glendining[3] described two cases of stomach carcinoma with secondary ovarian growth. In both observations cancer cells were present in the lumina of the Fallopian tubes as well as in the mucosal lymphatics. In discussing the origin of this interesting pathology Glendining assumed that cancer cells entering the lumina of the Fallopian tubes by their fimbriated extremities, became implanted in the tubal mucosa and from thence invaded the subepithelial lymphatics and the lymph vessels of the mesosalpinx. He finally concluded that the possibility of the origin of the tubal carcinoma from the ovarian growths by way of the lymphatics cannot be entirely excluded.

Sitzenfrey[18] reported an instance of carcinoma of the uterus associated with the presence of free bits of the uterine growth in the lumen of one of the Fallopian tubes. No evidence of carcinoma invading the tubal mucosa itself could be demonstrated in the Fallopian tube.

Schiller[17] added another observation of free cancer particles in the tubes of a specimen of primary carcinoma of the body of the uterus. The case presented many points of interest. The uterus contained an extensive advanced adenocarcinoma of the glandular type and the clumps of cancer cells lying free in the right tube showed the same histologic structure as the large uterine tumor. In some places both tubes exhibited the features of chronic salpingitis with marked chronic inflammatory changes of their walls. Carcinoma was not found to be present in the lymph channels in any portion of the specimen. It is interesting to note that the external uterine os was occluded. The patient was 49 years of age and the last menstrual period occurred six months before the operation. Schiller agrees with the opinion given by Sitzenfrey that secondary tubal carcinoma may arise from this source and that with a further migration of these particles implantation of this growth on the surface of the ovary and peritoneum may develop. This displacement of the tumor fragments into the tube may be explained by assuming that these particles were pressed into the tube by contractions of the uterus, and on the other hand, that the normal peristalsis of the tube and the action of its ciliated epithelium were not strong enough to resist this retrograde invasion.

In recent years disagreement as to the importance of the transtubal cancer dissemination has arisen in the American literature, while in the British and German literature less attention has been devoted to this problem. The question as to whether or not the transtubal migration of cancer cells plays a role in the spread of pelvic carcinoma has become a matter of controversy and it may be of interest to review briefly the most significant opinions.

Sampson,[13-16] in 1924, presented a fundamental study, dealing with the pathologic conditions arising from the implantation of tissue and epithelium which escapes through or from the Fallopian tubes into the peritoneal cavity. He had also shown that particles of malignant endometrial tumors, at times, escape into the lumina of the tubes or may be forced into as well as through them by manipulations of the uterus such as ungentle pelvic examination, curettage, and other surgical procedures. Convincing evidence was shown indicating that implantation of these fragments sometimes occurred in tubal mucosa, and on the surfaces of the ovaries and peritoneum. On the basis of these new findings and of his previous investigations, Sampson laid down several rules in the treatment of cancer of the body of the uterus to prevent its transtubal dissemination. He advised abdominal hysterectomy starting with the

ligation of the fimbriated ends of both Fallopian tubes, great care and gentleness in pelvic examination, and warned of the use of radium as well as of the abuse in employing diagnostic curettages.

In a later paper, Sampson[15] modified some of those rules, particularly his reaction toward the use of radium, and now recognizes the therapeutic value of the proper intrauterine radium application in carefully selected cases of carcinoma of the body of the uterus, in spite of some dangerous disadvantages occasionally occurring from its employment.

Norris and Vogt[7] reported the results of a study of 115 cases of carcinoma of the body of the uterus. Metastases were observed only in two instances in the ovaries and once in the tube; the great majority of the secondary growths were found in the pelvis. The authors are advocates of Sampson's endometriosis implantation theories and believe it is at least possible that a similar condition may occur in the case of carcinoma cells originating within the uterine cavity.

Sampson's conception of the significance of the Fallopian tubes as a noteworthy pathway for the dissemination of malignant tumors of the uterine mucosa was bound to cause much concern among the orthodox believers in the lymphatic route, and his findings and views were subjected to revision by subsequent authors.

Novak[8, 9] was among the first and strongest opponents. A critical analysis of Sampson's paper of 1924 as well as his own investigations led him to the opinion that Sampson has attributed too much importance to the occasional findings of free cancer particles in the lumen of the Fallopian tube. He expressed the belief that the description of those several cases upon which Sampson's views were mainly based presented no definite evidences for considering that these broken off particles are also responsible for the further spread of the cancer. In discussing the various routes by which the growths might have extended, he emphasized that they had been disseminated through the usual lymphatic channels: "certainly this route cannot be excluded, and, as this is the recognized route for cancer dissemination, it cannot be disseminated without much stronger evidence than is contained in Sampson's paper."

Robinson,[12] in a study on primary and secondary ovarian tumors, accepts only the lymph and vessel routes through which metastases may take place. He pointed out that the cancer tissue in secondary ovarian, tubal, and uterine carcinoma is located within the lymph spaces or blood vessels of the stroma, and that the lining epithelium of these organs presents a normal appearance. It was found that secondary ovarian carcinoma is characterized by the absence of any epithelial involvement, so that the differentiation between primary and secondary carcinoma of the generative organs, at least in the earlier stages, should not present a problem. Robinson believes that the contemporaneous appearance of malignant papillary tumors, within ovarian cysts and upon the surface of the ovaries, and similar growths of the uterine and tubal mucosa as well as the serosa covering these organs, "is due to the same biologic factors influencing variously located and metamorphosed epithelial centers of a common genetic source."

Offut[10] discussed the subject of the relationship of carcinoma of the body of the uterus and of the ovaries. The histories of 520 cases of adenocarcinoma of the body of the uterus and 616 cases of papillary cystadenocarcinoma of the ovaries in which operation had been performed in the Mayo Clinic from 1913 to 1930 were reviewed. In 11.9 per cent of the cases of carcinoma of the body of the uterus and in 8.6 per cent of the ovarian growths there was carcinoma in both organs. The specimens from 53 of these cases were chosen for intensive microscopic study which revealed 5 cases of primary uterine carcinoma with metastases to the ovary, 16 cases in which the lesion was found to be primary in the ovary and secondary in the uterus, 31 cases in which the situation of the primary lesion could not be determined and 1 case with apparently independent carcinoma in both organs. In 15 of these 53 cases, secondary involvement of the tube was present, and in "several" instances cancer cells were noted in the lumen of which lymph- and blood vessels were normal. In an attempt to determine the various possible modes of extension by which carcinoma might have spread in these cases from the uterus to the ovary and vice versa, Offut expressed the opinion that the Fallopian tube should be regarded as one of the routes through which cancer may be disseminated.

The following case is reported in some detail because a careful search of the literature has failed to reveal any case with a similar combination of pathologic findings, justifying the assumption of transtubal cancer dissemination.

CASE REPORT

A white female, 43 years of age, was admitted to the hospital, complaining of fullness and heaviness in the lower abdomen, shortness of breath, and of a painful swelling of the umbilicus.

The family history was essentially negative. Her father died of ileus; her mother died of myocarditis.

The patient had measles and chicken pox in childhood. At the age of 13, she is said to have been treated for "apex pulmonary catarrh," and thirteen years later she developed a tuberculous tendovaginitis of the right hand.

Menstruation had begun at 13 years of age, and for three years had been regular, lasting from two to three days, and was moderate in amount. At times there was pain in the back and in the ovarian regions. At 16 years of age she did not menstruate for three months, and then the periods had changed in amount and duration. They lasted only one to two days and were very scanty. The menstrual history showed that she passed an apparently normal menopause one year before admission, at the age of 42. There was no discharge except at menstrual periods.

She denied venereal infection, was unmarried, and never had been pregnant. Patient drank no alcohol and used no tobacco.

Her present illness dated back for about two years, when she had noticed a slowly enlarging swelling of the abdomen associated with some shortness of breath on exertion. She was fairly well until two weeks before admission when she first noted a small lump in her navel which grew larger, became distinctly painful, and had never retrogressed. She could recall no history of injury to the part but thought injury was probable. There was no discharge from the navel. Except for an increasing dyspnea there were no other subjective complaints.

On admission, general examination revealed a well-developed, fairly well-nourished female. The temperature, pulse, and respiration were normal, and the systolic blood pressure was 130 mm. Examination of heart and lungs was negative. The abdomen was found symmetrically distended and bulging due to the presence of a great deal of free fluid. The skin over the umbilicus was of a distinct dark, bluish discoloration, and slightly edematous, but freely movable over a more deeply situated, rather firm, nodular mass, about the size of a walnut. The mass was buried in the fatty tissues of this region, attached to the deeper structures and not well outlined. Serologic tests for syphilis, as well as urine and stools were negative; sedimentation rate and blood chemistry were normal.

Eight liters of clear, yellowish fluid were removed by paracentesis showing a specific gravity of 1.025 and alkaline reaction. The sediment contained an abundance of lipoid droplets. Following paracentesis, no masses could be felt abdominally, aside from the nodular swelling in the region of the umbilicus. The liver and the spleen could not be palpated. Roentgen ray examination of the chest and stomach revealed no changes. On rectoscopic examination, the mucosa was normal.

Gynecologic examination revealed normal external genitals; the hymen was intact, but permitted introduction of the examining finger and of a virgin speculum. Both lips of the portio were extensively eroded. The body of the uterus was normal in size, symmetry, anteflexed, firm in consistency, and movable. In the left adnexal region an indefinite mass was felt which could not be definitely made out because of some muscular rigidity and tenderness. No pathology was palpable in the region of the right adnexa. Some tenderness was obtained in the cul-de-sac of Douglas on firm pressure. A distinct, well-circumscribed, firm tumor mass about the size of a plum was felt in the cul-de-sac on combined vaginal and rectal examination. On the basis of the above clinical history and physical examination, a tentative preoperative diagnosis of ovarian carcinoma with peritoneal implantation was made. Surgical intervention was therefore recommended.

Operation.—Under lumbar anesthesia a long median incision was made from the symphysis, extending about 2 inches above the umbilicus and encircling the latter. After opening the peritoneum, the umbilical nodular mass was excised with the overlying skin. The peritoneal cavity contained a small quantity of serosanguineous fluid. The serous surface of several coils of bowel was covered with minute nodules and plaquelike elevations. These lesions were round or oval in shape and only slightly raised above the surface. They varied in size from a pin's head to several millimeters in diameter. The color was ochre yellow, but varied here and there from light yellow to light brown. The smallest tissue islets were very soft, and the larger, apparently older ones were of a firmer, somewhat rubbery consistency. A few similar elevations were also seen on the surface of the fundus of the uterus. The bottom of Douglas' pouch was filled with some loose, friable, and yellowish tumor material which was easily removed by hand. The peritoneal surface of Douglas' pouch itself, however, showed a smooth, glistening, and intact serous covering. No palpable or macroscopically visible metastatic nodules were observed in the liver or stomach, and the omentum appeared to be normal. There were some adhesions around both adnexa, especially around the region of the left ovary. The latter was found to be enlarged to nearly twice the normal size. The enlargement was due to a mass, very friable and soft in consistency and of greenish-yellow color. The ovarian tumor closely resembled a large cystic corpus luteum, but later proved to be a solid mass. The entire uterus and both adnexa were removed in the usual manner. There was some difficulty in enucleating the ovarian tumor from its dense adhesions because of the extreme friability of its tissue. The nodulus in the posterior cul-de-sac was found to be well circumscribed and of superficial character. There was no apparent connection with the cervix. Metastases to the retroperitoneal lymph nodes were not detected. Drainage of the paravaginal space was made by passing a strip of iodoform gauze into the vagina. The pelvic peritoneum and the sigmoid were united over the gauze strip, burying the stumps and causing complete peritonization. The omentum was brought down and the incision closed in layers.

The patient made an uneventful recovery, left the hospital twenty-two days after operation, and was referred for deep x-ray therapy. She reported at stated intervals, and her condition remained perfectly normal except for some moderate vasomotor disturbances which were treated endocrinologically. Nine months after the operation the patient had gained about twenty-five pounds. Pelvic examination made four years after operation was normal, there being no evidence of any recurrence of the carcinoma.

Pathology.—Gross examination: The specimen removed at operation included the uterus to which both tubes and ovaries were attached. In addition, there were two separate nodular masses about 3 and 4 cm. in diameter. The uterus was 7 cm. long, 4 cm. broad in its greatest transverse diameter, and 3.5 cm. in its anteroposterior diameter. Except for the above described tissue islets and some adhesions clinging to its surface, the perimetrium was smooth and glistening. The uterus was soft in consistency and the cavity was almost completely filled with a polypoid tumor mass arising from the anterior wall of the fundus. It was yellowish in color, very soft, and friable, and as big as an olive. The growth pointed downward, projected through the internal os and covered the endometrium. The mucosa lining the uterine cavity apparently had been replaced by a superficial carcinoma, presenting a whitish gray translucent color. The uterine wall averaged 1.5 cm. in thickness. The cervical canal was rather short, but the mucosa was apparently unchanged. The left ovary was transformed into a solid tumor mass 6 by 4 by 4 cm. and covered by numerous adhesions. The surfaces made by cutting showed it to be made up of a yellow, soft, friable mass, which appeared to contain fatlike substances not resembling ovarian tissue. The right ovary and Fallopian tube grossly appeared normal. The left Fallopian tube was 7 cm. long and covered by a few adhesions; its outer third was slightly dilated. The nodule excised with the umbilicus contained a cavity 2 cm. across and was filled with yellow reddish necrotic material. The tumor mass removed from the posterior cul-de-sac was solid and grossly appeared to be malignant.

Microscopic examination: The whole corporeal mucous membrane was found to be converted into an extensive papillary adenocarcinoma extending downward into

the internal os (Fig. 1). The neoplasm exhibited a high degree of differentiation. Some parts of the section presented a glandular appearance. Large and small groups of glands were seen. A gland was frequently separated from its neighbor by several layers of cylindrical epithelium, there being no intervening stroma. The gland cavities were lined by several layers of irregular cylindrical epithelial cells. The nuclei were oval, vesicular, and fairly uniform in size. There was no increase in chromatin, and only few if any mitotic figures were to be made out.

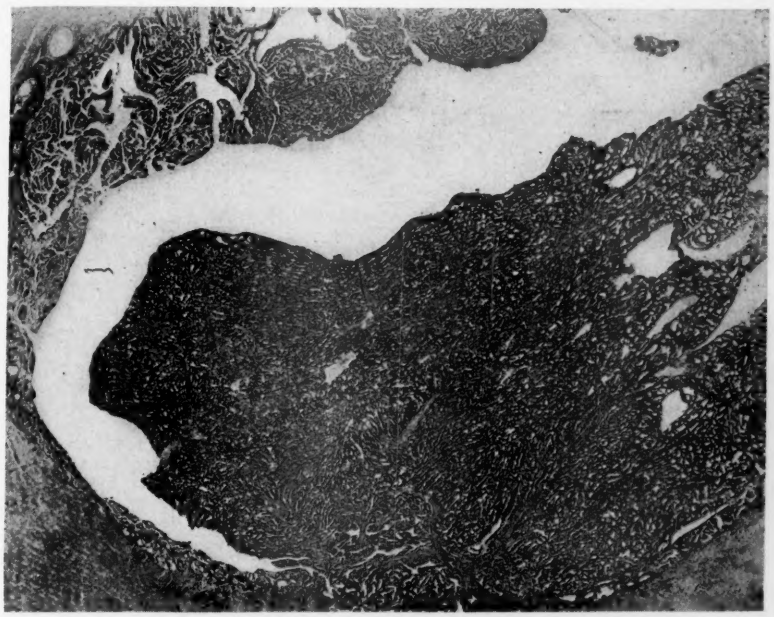

Fig. 1.—Photomicrograph of a section of the uterine tumor arising from the endometrium. (Hematoxylin and eosin; ×6.)

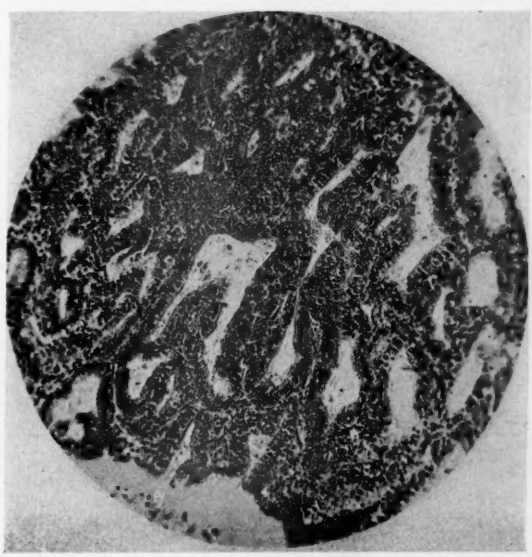

Fig. 2.—Photomicrograph of carcinoma shown in Fig. 1. Typical papillary adenocarcinoma of the body of the uterus. (Hematoxylin-eosin; ×70).

In some places the epithelial cells formed small cystic cavities having little treelike papillary excrescences extending into their lumina while in others the proliferating glandular epithelium tended more to the formation of small solid cell nests. The gland cavities, being entirely filled with the cells, had become obliterated (Fig. 2). These masses of cells closely packed together had large and small, oval, vesicular nuclei, and bore a remarkable resemblance to nodes of squamous epithelium. The concentric arrangement of the cells was strongly suggestive of the beginning formation of epithelial pearls. At no point could the carcinomatous process be seen invading the uterine muscle. The cervical glands presented their usual appearance.

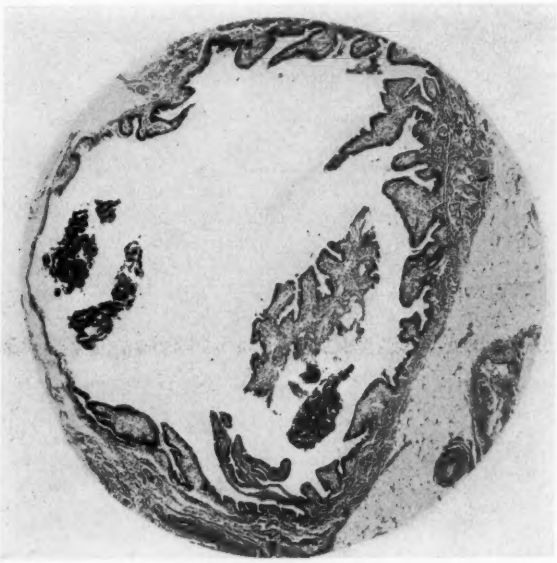

Fig. 3.—Photomicrograph of a cross-section of the left Fallopian tube showing three particles of the malignant tumor lying free in the lumen. (Hematoxylin and eosin; ×15.)

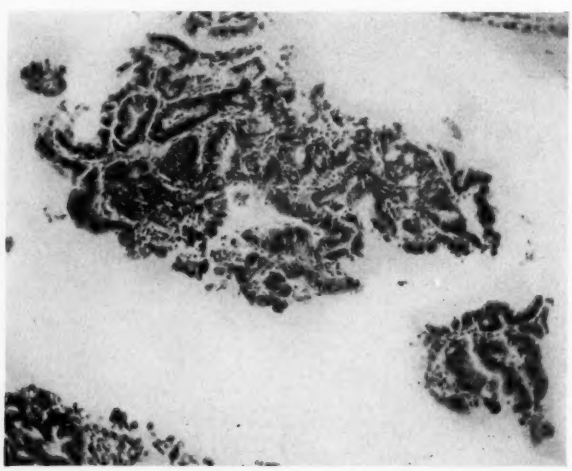

Fig. 4.—Photomicrograph of the tumor particles shown in Fig. 3. The particles of the malignant growth are of the same histologic structure as the primary tumor of the endometrium (Fig. 2) and the metastasis to the cul-de-sac (Fig. 5). (Hematoxylin and eosin; ×70.)

The polypoid endometrial growth, occupying the uterine cavity, showed the histologic characteristics of a papillary adenocarcinoma, sometimes approaching the squamous cell type, identical in appearance with that of the endometrium.

The outer portion of the left Fallopian tube was moderately dilated, and its muscular layers were slightly thinned out. The mucosal folds were found to be normal. The most striking characteristics in the sections were three particles of carcinoma, having the same histologic structure as those of the endometrium and of the polypoid growth. They appeared to be free in the lumen of the Fallopian tube (Figs. 3 and 4). Carcinoma invading the mucosa itself could neither be determined in this Fallopian tube nor was it found in the veins or lymphatics in any portion of the specimen.

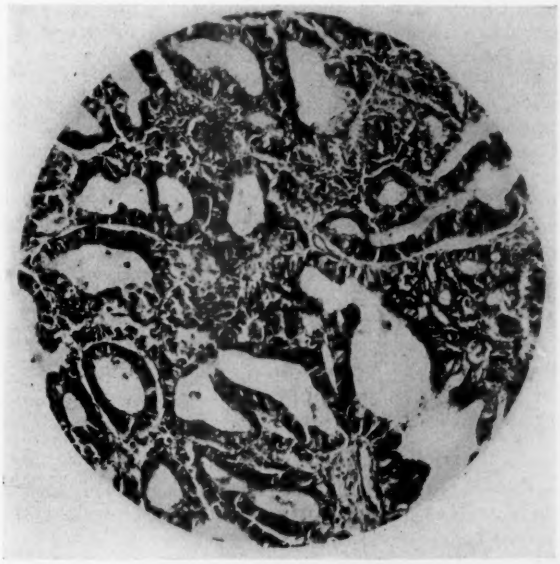

Fig. 5.—Photomicrograph showing a portion of the nodule removed from the cul-de-sac. The histologic structure is similar to that of the large uterine tumor (Fig. 2) and also to the particles of the tumor found free in the lumen of the left Fallopian tube (Fig. 4). (Hematoxylin and eosin; ×70.)

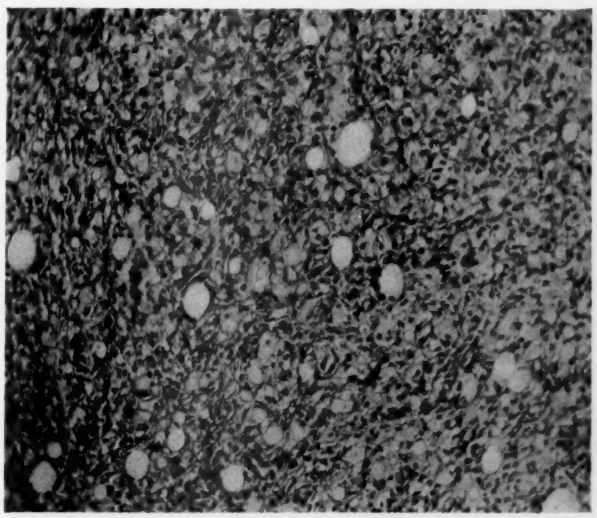

Fig. 6.—Photomicrograph of a section of a portion of the left ovary. It shows well the foamy appearance of the pseudoxanthoma cells. (Hematoxylin and eosin; ×70.)

The tumor nodule removed from the posterior cul-de-sac presented a histologic structure of a well-differentiated glandular carcinoma, similar to that of the uterine growth as well as to the free tumor particles in the lumen of the tube (Fig. 5). The growth was found to be sharply demarcated from the surrounding tissue, although not definitely encapsulated. At the periphery and especially in the center of the nodule, numerous red blood clots were observed to contain spindle-shaped vacuoles due to cholesterin crystals, and needles of fatty acids. The tissue surrounding the tumor showed a marked small round cell infiltration.

Sections through the left ovary showed that the tissue was edematous, with chronic inflammatory changes, and diffusely infiltrated with fairly large, elongated oval to round cells (Fig. 6). At times, when grouped in masses, they were compressed into polygonal shape. At first, in the fresh state, the protoplasm seemed to be loaded with an abundance of small droplets of fatlike substance. Treated with ordinary reagents that dissolve out the fat (alcohol, xylene), the cytoplasm became a fine, areolar network, giving a foamy or highly vacuolated appearance. This impression was given support by the fact that abundant fatlike material was demonstrable in these cells by means of differential staining. The fatlike substances consisted of granules or round droplets, and at times crystals in small rods or fine needles united in clusters were seen. As far as could be made out by studying various stages of transition, these cells might arise from cells of the inflammatorily infiltrated connective tissue, and in a more advanced stage their cytoplasm was found to be increased. In the larger round cells, the cytoplasm became greatly diminished in amount and limited to small foamy rests; most of the nuclei had entirely disappeared. Those which remained, showed different stages of necrotic shrinkage, the nuclear material being condensed into a single round globule, staining uniformly and deeply with hematoxylin. These cells, showing fatty degeneration, represented the sequel and end product of a pathologic change, affecting the cells of the connective tissue. They may be considered as a distinct, pigment free type of cells of connective tissue origin, the pseudoxanthoma cells.

The cavity below the umbilicus was lined by inflammatory granulation tissue which, for the most part in its deeper portions, was also converted into masses of pseudoxanthoma cells, identical with those described in the left ovary. In a few places the tissue contained large areas of extensive necrosis with fragments of leucocytes which had undergone necrosis by karyokynesis.

Careful examination of numerous microscopic sections through the right ovary and the right Fallopian tube revealed no change but a few areas of round-celled infiltration. The right tube presented no carcinoma in its lumen, mucosa, veins, and lymphatics in any portion of the specimen.

We have in this case a typical papillary adenocarcinoma of the body of the uterus associated with a secondary growth in the posterior cul-de-sac. Bits of the malignant tumor were found free in the lumen of the left tube near its fimbriated end. The ovarian tumor and the umbilical nodule showed chronic inflammatory changes, extensive necrosis, masses of pseudoxanthoma cells, and the absence of carcinoma.

DISCUSSION

From a review of the literature, it would seem that the occasional finding of free and implanted cancer particles in the Fallopian tubes in cases of uterine and ovarian cancer is not as uncommon as was formerly believed. The supposed rarity of the condition is more apparent than real and may be due to a neglect in making routine microscopic examinations of the Fallopian tubes which, at the first sight, appear to be normal.

According to the reported cases, cancer cells and particles may enter the Fallopian tubes by either or both ends: (a) malignant material originating from ovarian and other intraperitoneal tumors may be wafted into the lumina of the tubes by their fimbrias; (b) cells and bits

from malignant tumors of the endometrium are forced into the uterine openings of the tubes by spontaneous, colicky contractions or manipulations of the uterus.

Spontaneous contractions of the uterus occur during menstruation and may also be caused by the stimulus of the pathologic uterine contents. Occlusion or narrowing of the internal os by the uterine growth or blood clots as well as retrodisplacement may assist in causing the backflow.

Manipulations of the uterus which may play a role in the intratubal spread of cancer include bimanual pelvic examination, intrauterine instrumentation as well as hysterectomy.

The further transportation of the malignant material within the lumen of the Fallopian tube occurs: (a) by the normal tubal peristalsis similar to the migration and final implantation of the fertilized ovum, being carried down the tubes toward the uterine cavity; (b) by antiperistaltic contractions of the tube passing cancer cells and tumor particles toward its fimbriated end, and at times, into the peritoneal cavity.

That the Fallopian tubes are capable of muscular contractions and peristaltic movements has been distinctly demonstrated by Rubin's peruterine gas insufflation and the kymograph.

Menstrual regurgitation of blood, containing malignant material and retrograde peristaltic movements in the Fallopian tubes should be regarded as noteworthy factors in causing this displacement, as about one-third of women suffering from carcinoma of the body of the uterus had not passed the menopause. 36.3 per cent of Stacy's cases[19] were premenopausal; Norris and Dunne[6] found 30.5 per cent; Masson and Gregg,[4] 33 per cent. Crossen and Hobbs[1] observed that menstruation persists longer in women in whom carcinoma of the fundus develops. Furthermore, most patients having passed the menopause just before onset of symptoms are included in the postmenopausal group.

The implantation of cancer cells escaping from ovarian carcinoma upon the surface of the various structures in the pelvis is of common occurrence. The readiness with which particles of endometrial tumors may sometimes become implanted upon the tubal mucosa, the surface of the ovaries and the pelvic peritoneum has long been assumed by numerous authors but never until recently has this phenomenon been actually demonstrated. Careful microscopic investigations by Sampson disclosed the histogenesis and progression of these implants; their distribution was often found to be similar to that of the benign endometrial implants.

It is noteworthy to mention here that some danger exists in the spread of malignancy into the Fallopian tubes when such exists in the uterus when diagnostic and therapeutic manipulation and instrumentation are used.

CONCLUSIONS

1. The presence of free cancer particles in the normal Fallopian tube may indicate the pathway of spread of pelvic cancer.
2. A case is reported illustrating the spread of pelvic carcinoma by way of the Fallopian tube.

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730 West Cornelia Avenue

THE ERYTHROCYTE SEDIMENTATION REACTION DURING PREGNANCY*

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THE sedimentation of erythrocytes is a characteristic of whole blood in both health and disease. The sedimentation rate is a means of expressing the velocity at which the red blood corpuscles separate from the blood plasma. The separation of these elements of the blood was noted in ancient times, and the knowledge of this property appeared in the writings of Galen. John Hunter, in 1855, noted the separation of the blood corpuscles from the blood plasma and recognized the increase in the rate of separation of these elements in disease. Robert Fahreus, in 1919, however, gave the first serious academic thought to the problem. It is interesting to note that his first observations on the sedimentation properties of red blood corpuscles were made during the natural course of pregnancy in an attempt to establish a laboratory test for the early diagnosis of pregnancy. Since this re-introduction to modern medicine, a vast amount of experimental and clinical work has been performed, and the results of this work dealing with the principles of erythrocyte sedimentation are worth stating.

THREE PHASES OF ERYTHROCYTE SEDIMENTATION

In the process of sedimentation three stages are commonly recognized. The initial stage, a period of aggregation, is one in which there is an agglutination of small groups of erythrocytes into rouleaux. This stage usually takes place during the first few minutes but is subject to variation. In extremely stable bloods, those in which the sedimentation will progress very slowly, the aggregation of cells proceeds slowly. In specimens in which a rapid sedimentation rate will be found, the aggregation

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of units can be directly observed. A parallelism, therefore, exists between the degree of aggregation and the sinking velocity of the red blood corpuscles. Fahreus stated in his original work that this was the most predominant factor in the sedimentation reaction. The period of aggregation has been explained on the basis of autoagglutination, various chemical changes in the blood, and electrophysical principles which I will not discuss at this time.

The second stage of the sedimentation reaction is the period of actual sedimentation. It is this stage which we commonly observe and record, and in which the variations noted in health and disease are characteristic.

The third stage is the period of packing. At this time the red blood corpuscles have progressively piled up upon each other. Active sedimentation has become arrested due to the passage of all of the corpuscles through the suspensoid. There is now practically complete separation of the blood plasma and the erythrocytes. At the end of this period the volume of cells closely approaches the volume following centrifuging. In blood specimens which are stable, there is usually a slow, constant rate of fall in which the separate stages cannot be recognized clearly and which may require several days before the packing period is reached. In these instances, when charted, the graph depicting the separation of the corpuscles from the plasma is a diagonal but straight line. In specimens having a rapid sedimentation rate there is usually a precipitous drop in the curve at the onset of active sedimentation and a rather abrupt horizontal swing when the period of packing begins. In the latter cases the period of packing usually begins prior to the customary hour's observation, and if the rate of fall is calculated upon this one observation alone, true results will not be obtained. The latter reading will be sufficient to reveal only that the rate is rapid by virtue of completion of the period of active sedimentation in one hour or less. In general, all rapidly falling specimens will tend to fall within a range, at the end of one hour, which is related to their actual cell volumes.

EXPRESSION OF SEDIMENTATION RATE

There are two common means of expressing the rate of sedimentation. The Westergren method expresses the rate in terms of millimeters per hour and only one reading is observed. In this method a 200 c.c. glass pipette having a 2.5 mm. internal bore (diameter) is used. The Cutler method expresses the rate in millimeters per minute. A 5 c.c. glass tube graduated in millimeters and having an internal bore of 15 mm. in diameter is used. Observations are made each five minutes for the duration of one hour, and a differential rate of fall is thus obtained. The period which is used as the criteria for the expression of the rate is that five-minute period in which the greatest actual fall takes place. This rate is then simply converted into millimeters per minute. Although the latter method requires constant attendance during the one hour period of observation, it has a distinct advantage: The most important phase of the sedimentation reaction is directly observed. By projecting the distance fall against the time interval upon a properly constructed chart the action of sedimentation becomes *graphic*. This we regard as most important. During the course of disease successive super-

imposed graphs of the sedimentation rates in many instances augur recovery or remission. With a little experience the type of curve speaks for itself and no rate need be calculated. We believe that mere factual expression of a sedimentation rate based upon either one observation or upon the most rapid rate of fall within a narrowly delimited space of time is practically valueless clinically. We realize, however, that in the absence of graphic comparisons it is a necessary medium for the expression of the sedimentation rate.

SEDIMENTATION RATE AND BLOOD FIBRINOGEN

It would seem that there should be some quantitative chemicophysical change in one or more constituents of the blood responsible for the varying sedimentation rates. As has been stated, Fahreus considered the degree of aggregation of the erythrocytes directly related to the varying rates of fall. The radius of the corpuscles and their specific gravity as well as the specific gravity of the plasma is said to affect the rate. While there are many factors that may be considered, all investigators agree that the sedimentation of erythrocytes in whole blood is bound with the properties of the plasma alone. This is simply evidenced by crossing the clear plasma from a blood specimen in which there had been a rapid sedimentation rate and the washed cells from a specimen in which the rate was slow. The rate is invariably rapid. When the washed cells from the specimen with the rapid rate of fall are placed in the plasma from the "slow" specimen, the rate is slow. In the plasma most evidence points to the protein fractions as the responsible factors. Of these, the serum fibrinogen has been the most constant and reliable index. The serum globulin bears a close relationship with the fibrinogen and both are directly proportional to the sinking velocity of the erythrocytes while an inverse relation exists with the plasma albumin.

FACTORS CAUSING VARIABILITY IN READINGS

The technical procedures related to the sedimentation reaction are simple, but there are a few interesting experimental results which have a direct clinical bearing upon the validity of any observation. A knowledge of these should be familiar to anyone using this laboratory procedure. (1) Because of the changes that added electrolytes may bring about in the stability of the blood, Rourke and Plass deemed it advisable to determine the effects of the various anticoagulants in common use, in view of adopting a substance which had no effect upon the suspension stability of the blood other than to prevent the blood from clotting. Sodium fluoride (5 mg. per 5 c.c. of blood), potassium oxalate (14 mg. per 5 c.c.), potassium citrate (10 mg. per 5 c.c.), and 5 per cent sodium citrate (1:4) were found by them to produce slight slowing of the sedimentation rate in proportion to the concentration used, although these did not affect the trend of results. Heparin (1 mg. per 5 c.c. of blood) was found to be ideal, for the presence of more than sufficient quantities to prevent the blood from clotting did not further alter the rate of sedimentation. Other investigators, using smaller quantities of the electrolytic anticoagulants, separately or combined, found no appreciable variation in the rate. It would seem, therefore, that any of

the above-mentioned anticoagulants will not greatly affect the reliability of the sedimentation rate as far as clinical application is concerned. (2) Rourke and Plass found that after collection of a blood sample and after anticoagulants were added, if the specimen were permitted to stand at room temperature for six to twelve hours, there was no change in the rate of sedimentation after re-mixing. (3) With an increase in the temperature there is a corresponding increase in the sedimentation rate. However, within the range of normal room temperature (20° to 25° C.), there is not sufficient variation to necessitate correction. (4) A slight inclination of the sedimentation tube from the vertical will cause a great increase in the rate of fall. (5) Neither the bore of the tube nor the volume of blood used has any effect upon the sedimentation rate, provided the height of the column of blood remains the same. (6) There is no change in the rate after centrifuging blood to which an anticoagulant has been added and then re-mixing.

NORMAL VALUES FOR SEDIMENTATION RATES

The sedimentation of red blood corpuscles is a characteristic of normal blood which has slight physiologic variations in health and greater deviation in disease. The slowest rates are found with the blood of the newborn in which rates averaging 0.5 mm. per hour have been reported. In the normal healthy adult the ranges vary between 3 and 9 mm. per hour for men and from 3 to 13 in women although rates less than three are considered within the normal range but are uncommon. In most instances during disease, local or systemic, the variation from normal is marked. Physiologic increases in the rate of sedimentation have been observed and this occurs during pregnancy.

* * * * *

The work upon which this report on the sedimentation reaction during pregnancy is based was performed at Cleveland Maternity Hospital upon patients registered in the Maternity Hospital Out-Patient Department.* In performing the tests, 5 c.c. of whole blood were used to which three drops of a saturated solution of potassium oxalate were added as the anticoagulant. At the same time erythrocyte, leucocyte, and hemoglobin determinations were made. The Cutler 5 c.c. sedimentation tube was used and all actual observations were recorded on the Cutler graph at five-minute intervals for one hour. Theoretical corrections were based upon calculations of the cell volume, using a modification of the Rourke-Ernstine correction chart. In a few instances correction was based upon the percentage of normal erythrocyte count.

Inasmuch as most of the patients' first visit to the Maternity Clinic was rather late in the course of pregnancy, our studies have not been sufficiently complete prior to five months to report. However, from reliable reports in the literature the changes in the rate of sedimentation first occur during the latter part of the second month, and 99 per cent of all pregnant women have a definite increase in the third month. Fahreus' figures based upon 100 normal pregnant women show an average fall of 17 mm. per hour during the second month, 24 mm. during the third month, 29 mm. during the fifth month, and the rate thus increases

*Technical Assistance of Miss Rose Ketteringham.

progressively to an average fall of 45 mm. per hour at term. Our work does not reveal rates as rapid as these. Fig. 1 shows the average fall of all cases during the course of pregnancy. On this and subsequent graphs the time interval appears along the top of the graph and the number of millimeters' fall (degree of sedimentation) is denoted on the left. During the fifth month, there is an average fall of 14 mm. with a variation of 3.5 mm. (see Table I). During the sixth month, the fall varies between

TABLE I

DURATION OF PREGNANCY	AVERAGE SEDIMENTATION IN MILLIMETERS	VARIATION IN MILLIMETERS (PLUS OR MINUS)
5 mo.	14.0	3.5
6 mo.	19.0	4.0
7 mo.	22.0	3.0
8 mo.	22.5	3.5
Term	24.0	3.5
Second day post partum	27.5	9.0
Seventh day post partum	25.5	9.0
6 weeks post partum	12.0	20.0

17 and 21 mm. with an average of 19. During the seventh month between 20.5 and 23.5 mm., average 22; between 17 and 26 during the eighth month although the majority vary between 21 and 24.5, average 22.5 mm. At term the distance fall is between 22 and 25.5 mm. with an average of 24. As you will note by the curves representing the sinking velocity of the erythrocytes there is a progressive increase in the average rate of fall during the ante-partum course. In the majority of cases, the greatest activity occurs between ten and twenty minutes and varies between 2 and 4 mm.

Post partum, on the second day (Fig. 2), in many cases there is a sharp increase in the sedimentation rate although the average of all cases shows a further fairly even progression over the last ante-partum rate. There is little change on the seventh day after delivery although in all instances, barring complications, the actual one-hour fall is slightly less. The graph shows the distribution of the differential rates of fall. The average is 27.5 mm. per hour with a variation between 23 and 32. The distribution five days later shows little change. In both instances the curves show an early tendency toward the vertical and the three periods of the sedimentation reaction are more than suggested. The essential difference in the post-partum curve from the ante partum is due mainly to a more active fall in the early stages, in other words the period of active sedimentation takes place more promptly; the first stage, the period of aggregation of the erythrocytes, is more rapidly completed. In general, on the second and seventh post-partum days, the greatest actual fall per one five-minute period varies between 3 and 17 mm., but the greater proportion fall between 5 and 6 mm. This fall occurs during the ten- to fifteen-minute period although the most active period in many cases occurs in less than ten minutes.

In operative cases such as cesarean sections, the rate of fall is more rapid during the immediate post-partum course. This is probably related to the added trauma to the tissues. There is no consistent variation in the sedimentation rates in toxemias of pregnancy either ante or

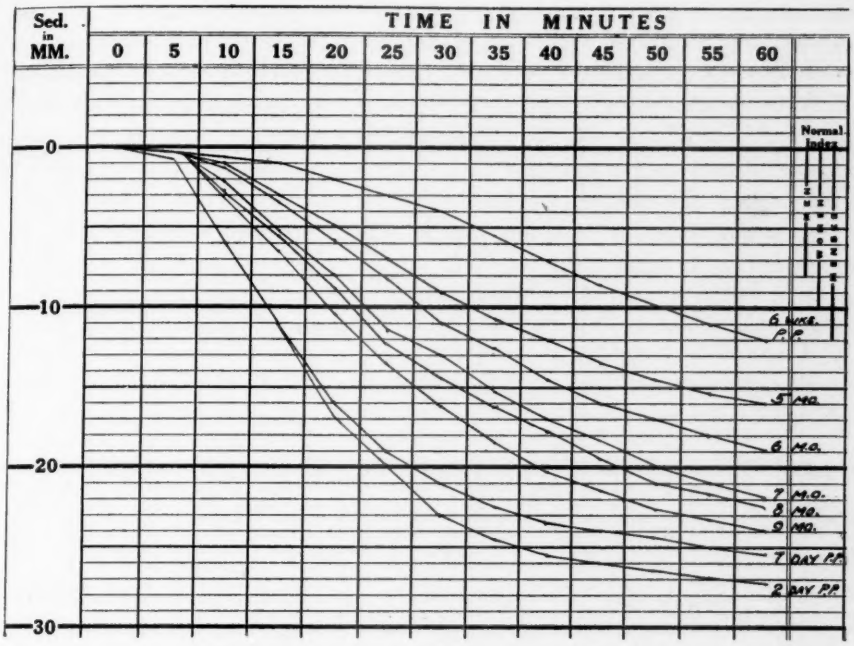


Fig. 1.—Average fall during pregnancy, actual.

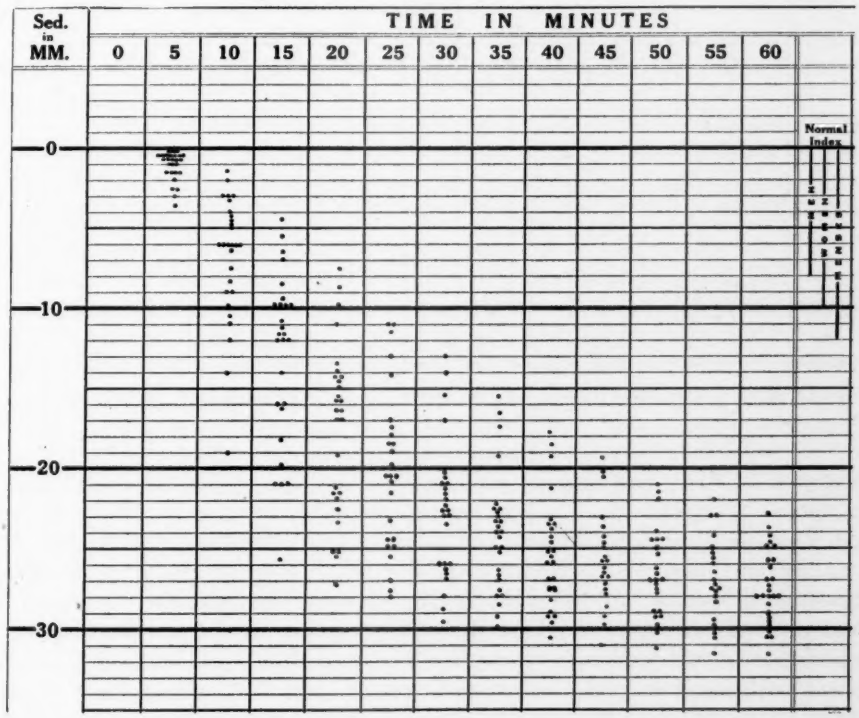


Fig. 2.—Distribution rates of fall, second post-partum day, actual.

post partum. Most acute infectious states, with or without a febrile reaction, are accompanied by an added increase in the rate of sedimentation during pregnancy. In many instances, however, cases which are obstetrically morbid are not associated with an increase in the normal expected sedimentation rate. These include morbidity due to cystitis, retained lochia, and common cold. Pyelitis, puerperal sepsis, and phlebitis are characterized by a rapid rate.

At the end of the puerperium, six weeks post partum, the rate of sedimentation again approaches normal. Seventy-two per cent are reported to have fallen within the normal range. In our series there is a wide variation, but the average fall at the termination of one hour is 12 mm., and there is the tendency of the projected graphs to assume a straight but diagonal line. This type of projection is a normal type or means a quiescent state in a previous infectious process.

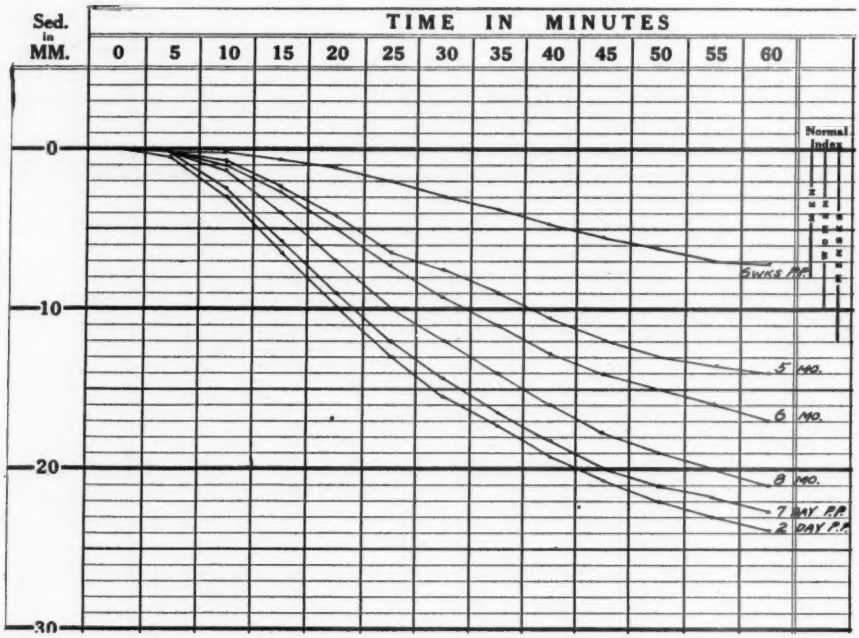


Fig. 3.—Sedimentation reaction during the course of normal pregnancy, one individual.

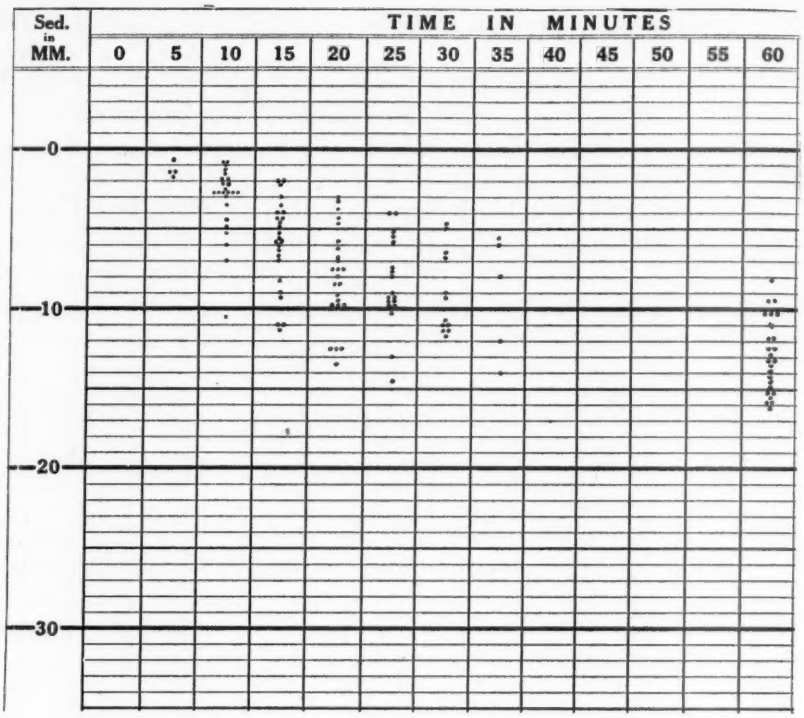
The rapid rate of the sedimentation of red blood corpuscles in pregnancy is said, by various investigators, to be due to a combination of factors: A physiologic leucocytosis produces an increase in the fibrinogen content of the blood; an anemia of pregnancy which is thought to facilitate an increase in the sinking velocity of the cells by virtue of the diminished number of particles in the suspensoid, therefore the mean *free* path of such particles becomes greater and consequently the rate at which they settle is increased. Other factors include: an increase in the blood volume, a decrease in the cell volume, and the absorption of the products of cell activity into the blood stream. Most reports are in accordance, however, no matter by what mechanism, that the rapid rate of

sedimentation during pregnancy is related to a physiologic increase in the plasma fibrinogen, and in some instances this is as much as a thousandfold.

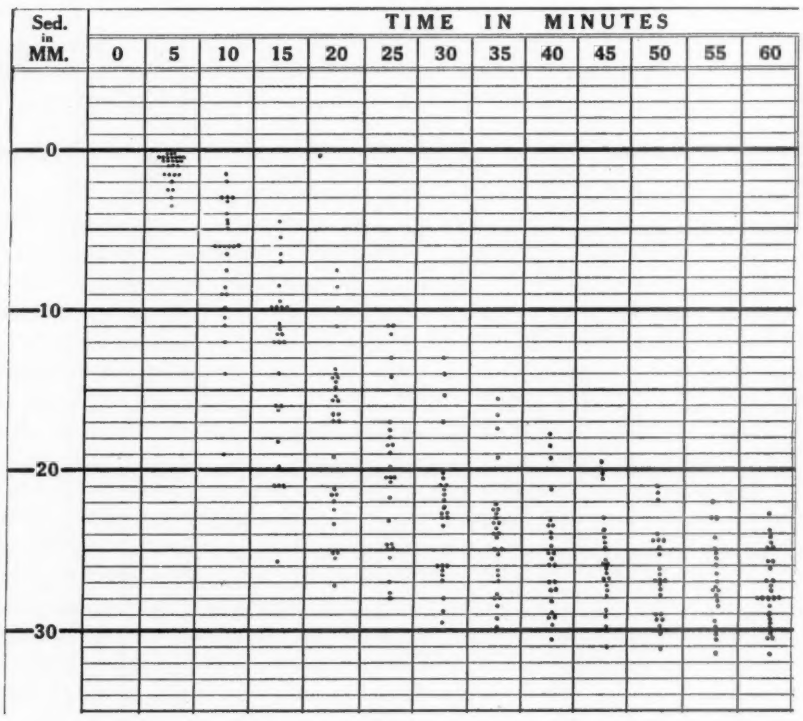
Fig. 3 illustrates the variation in the sedimentation rates during the course of pregnancy in one individual and serves to illustrate the value of graphic comparisons. I will not cite the leucocyte, erythrocyte, hemoglobin, and cell volume values which correspond to each curve, for I wish to discuss any relationship which might or might not be present later.

CORRECTION

In presenting the picture of the sedimentation reaction during pregnancy and the puerperium, it must be noted that all rates were actual and no reference was made regarding correction for anemia. The principle of any correction is based upon allowing for a variable item in order to state the results in terms of a normal constant. In the sedimentation reaction, corrections tend to aim at reducing an actual observation to an estimated value at a standard red blood corpuscle concentration in order to eliminate the variable factor, the degree of anemia. The cell volume has been used by most investigators in correcting sedimentation rates for anemia. In the normal individual there is supposedly a close correlation between the cell volume and the erythrocyte count, and the experimental error is but 0.5 per cent in the former and 5 per cent in the latter. By laboratory dilution experiments with normal bloods curves have been calculated and charts devised whereby the sedimentation rate of any blood specimen may be quickly corrected for anemia. The objection to these is that the normal range for cell volume varies widely among normal individuals. The variation is accentuated during pregnancy, and there is no constant reliable correlation between the erythrocyte count and the cell volume; a very slight tendency exists but no more. In most instances, for any one cell volume there is a variation of a million or more erythrocytes by count. Correlation between the cell volume and the hemoglobin content of the cells follows a slightly closer relationship but even here the average deviation for a given cell volume is 15 per cent hemoglobin. In fact during pregnancy there is no reliable relationship between the erythrocyte count and the hemoglobin content in the same specimen. The lack of actual correlation between any of the above variants therefore introduces three separate variables (cell volume, hemoglobin content, erythrocyte count) which should be taken into account for any reliable correction. Therefore, in an attempt to evaluate the efficacy of correction of actual sedimentation rates for anemia during pregnancy by one or all variable factors, we have been struck by the dissociation rather than the association of the elements concerned. We find that during pregnancy the value of corrected sedimentation rates in delivering a more accurate impression of the true trend of results is a misconception. Fig. 4 is a comparison of the actual and the corrected rates. The corrections were calculated from the cell volume. In most instances the corrections were carried out during the period of actual sedimentation only. The corrected rates at the end of



A.



B.

Fig. 4.—Comparison of actual and corrected rates of fall, second post-partum day.

one hour do not give a true picture inasmuch as the period of packing had already begun and the results are therefore grouped into a smaller range.

Regarding correction I quote Fahreus: "A comparative investigation between the number of corpuscles and the sinking velocity carried out on a great number of clinical cases shows the concentration of the corpuscles to be of less importance than dilution experiments would lead one to suspect. There is a factor counteracting the rapid sinking in anemic conditions which probably stands in connection with the fact that the blood corpuscles have relatively less tendency to aggregate in the blood which is sparse in corpuscular elements. In other words, the disadvantage of cell dilution experiments is that there is no proof that in the body a change in the cell volume or cell count occurs without a simultaneous alteration in the plasma which might itself affect the sedimentation rate."

CONCLUSIONS

1. There is a progressive increase in the sedimentation rate during normal pregnancy. There is no alteration in this rate associated with toxemias of pregnancy.

2. During the puerperium the sedimentation rate returns to normal in approximately 75 per cent of cases and tends toward normal in the remainder. The change begins after the second post-partum day.

3. The increased sinking velocity of the erythrocytes during pregnancy is related to an increase in the plasma fibrinogen fraction of the blood.

4. Sedimentation is the result of the interplay between many forces and different factors may have importance in different cases so that the problems of correction for anemia are complex. We believe "the observed result is the true one and the calculated one is based on experiments which have only a presumptive counterpart in nature."

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10515 Carnegie Avenue

THE ROLE OF DEEP CAUTERIZATION IN THE PREVENTION OF CANCER OF THE CERVIX

A Report of Ten Thousand Cases

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(From the Department of Gynecology, University of Pittsburgh)

SINCE the publication of Hunner's[1] memorable paper in 1906, cauterization of the cervix for the treatment of chronic cervicitis has been practiced in our* Clinic.

TECHNIQUE

After trying different methods of cauterization Dr. Huggins and I, in 1914, began using consistently the present technique of deep cauterization of the cervix in our *operative* cases. The main purpose was the elimination of cervicitis, but the prevention of cancer, if possible by this means, was a strong motive in the program.

In 1924, I[2] published the technique of deep cauterization, the after-treatment, and some histologic observations. This is not an office procedure and is done under anesthesia, usually in conjunction with other operative procedures. Routine postoperative dilatations must be done for at least ten weeks after deep cauterization. Postoperative dilatations are not necessary when subtotal hysterectomy is done, but the cervix is permitted to heal with obliteration of the canal.

The serious results of cauterization of the cervix such as cellulitis, peritonitis, and so forth, which are stressed by some authors, have not been a serious problem in this series. They are due in most instances, I believe, first to incomplete cauterization, thereby leaving a zone of infected glands beneath the cauterized tissue (Fig. 2); second, to cauterization in the presence of unrecognized subacute or chronic infection of the upper genital tract; and third, failure to carry out the proper postoperative care.

Deep cauterization was selected because sections of the cervix showed that the inflammatory process is frequently deep seated and that it is necessary to cauterize deeply in order to eliminate it. In practicing deep cauterization some of the shortcomings of superficial cauterization are disclosed that are not generally known. In cervices that have been cauterized superficially, sections taken immediately afterwards, or after healing has taken place, reveal too frequently that the deep glands have not been destroyed (Fig. 2) and that they are sealed in by the healing process and extensive cyst formation may result. In reoperating on these patients, it is found that many of these cervices are riddled with cysts that are often not evident until deep incisions with the cautery blade are made, and mucus and mucopus are discharged. We use superficial cauterization only when we feel that the infection

*This paper is presented as a memorial to my former Chief, Dr. R. R. Huggins, who initiated and planned this survey which was made possible through the financial support of the Spang Cancer Research Fund. His untimely death occurred before it was well under way.

is superficial, as in the so-called congenital pseudoerosions, sterility, and eversions soon after the first delivery, for lacerations with eversion of mucosa then furnish conditions that predispose to infection, but cervicitis has not yet occurred or is only superficial.

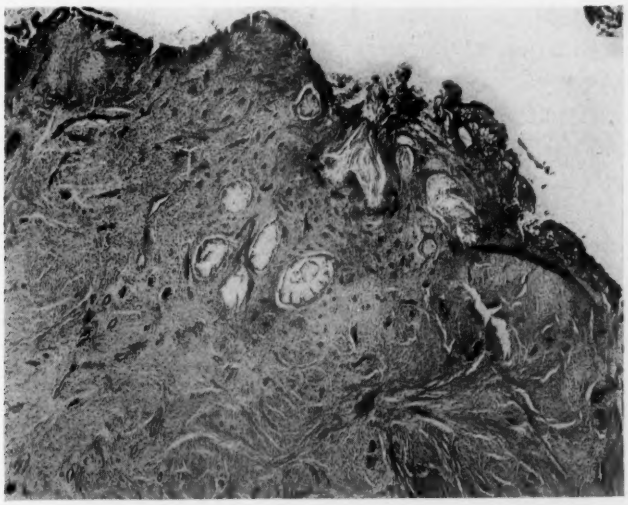

Fig. 1.—Photomicrograph of a section of an erosion after deep cauterization. Note the destruction of the glands.

Fig. 2.—Photomicrograph of a section of an erosion after light cauterization. Note the zone of noncauterized glands beneath the cauterized zone.

RELATIONSHIP OF CHRONIC CERVICITIS TO CANCER

For years chronic infection has been thought to be a factor in the occurrence of cancer of the cervix, largely because of the high incidence of women who have borne children among those with this type of cancer. In an analysis of 150 cases of cancer of the cervix, in 1927, the author found that 92 per cent had borne children. In the same series, in only

11 per cent was the cancer confined to the cervix. In our series it was learned that there are no symptoms of early cancer, for many of these cases were hopeless when the first symptoms occurred. We stated at that time, thirteen years ago, that the hope of control of cancer of the cervix lay not in the method of treatment but in early diagnosis by periodic examination of women, and in the prevention of cancer by adequate treatment of the pre-existing lesion, chronic cervicitis. Or, even better, the prevention of cervicitis by the proper treatment of the cervix after delivery. That is still our belief.

It is our belief and experience that a cervix, healed and free of infected mucosa (Fig. 3) is no more liable to develop cancer than the surrounding vaginal mucosa.

Fig. 3.—Photomicrograph of a longitudinal section of the cervical canal healed after cauterization. Note absence of glands, and the presence of squamous epithelium which covers the lower portion of the cervical canal in the healing process.

In order to prevent cancer of the cervix, it was felt that an effort should be made to eliminate chronic infection and inflammation from the cervix, and that this was possible only by complete removal of the gland-bearing portion of the cervix or by its destruction by deep cauterization (Fig. 1). Deep cauterization is less time consuming than amputation of the cervix. It is a simple, rapid, bloodless method, and this is important in long gynecologic operations.

Since 1914 the cervix has been cauterized routinely in all operations for chronic tubal infection, for the cervix is usually the source of these infections; in all subtotal hysterectomies; and in all patients with cervical leucorrhea sufficient to warrant radical treatment. The oppor-

tunity was used to clean up the infected cervix in any patient on whom operation was necessary for other conditions (Table I).

TABLE I. TYPE OF OPERATIONS

Cauterization alone	335
Cauterization and radium (in uterine cavity)	120
Cauterization and plastic surgery	629
Cauterization, plastic surgery, and laparotomy	323
Cauterization and laparotomy (other than hysterectomy)	1071
Cauterization and hysterectomy (subtotal)	665

CANCER OF THE CERVICAL STUMP

It has been found by many observers that cancer of the stump of the cervix after subtotal hysterectomy constitutes 2 to 5 per cent of all carcinomas of the cervix. In our 150 cases, there were four, or 2.66 per cent. This does not give any idea of what percentage of cervical stumps will develop cancer. Neilson[3] reports that statistics in 17,139 cases of subtotal hysterectomy show subsequent stump cancer in 67, or 0.39 per cent. He states that the incidence may be 1 to 1.5 per cent.

The increased mortality of total hysterectomy throughout the country will more than counterbalance the loss of patients from cancer of the cervical stump. The technique of subtotal hysterectomy, as I[4] advocated in 1926, consists of deep cauterization of the cervix regardless of whether it appears normal or not, followed immediately by laparotomy and subtotal hysterectomy. The supravaginal amputation is made low down near the attachment of the sacrouterine ligaments, and crosses the cauterized and sterilized cervical canal. Thus the cervical mucosa is destroyed, the canal is sterilized, hysterectomy is made safer and future trouble with the stump is practically eliminated. To cauterize or cone out the cervical canal from within the abdomen, as practiced in some sections, is not sufficient, for cancer usually occurs in the erosions or at the junction of the squamous and columnar epithelium on the portio.

SURVEY

In 1929, Dr. Huggins[5] reported 2,985 of our cauterization cases, with no knowledge, up to that time, of the development of cancer of the cervix in any of these patients, but no follow-up study had been made. In the same year, Pemberton and Smith[6] reported that in 5,952 operations on the cervix, including 1,408 cauterizations, 5 cases of cancer had developed and none had occurred in the cauterization group. (Only 20 per cent of their total series were followed either by letter or examination.)

Deep cauterization has been gradually adopted by those in the Gynecological and Obstetrical Departments of the University of Pittsburgh Hospitals. There is now a series of 10,000 cases over a period of twenty-five years. A follow-up study was undertaken to determine the incidence of cancer in the cervices so treated.

RESULTS OF SURVEY

Data were secured concerning 3,143 patients, and 1,341 of them returned for examination. The time interval after cauterization was from

one to twenty-four years. There were data on 771 subtotal hysterectomies.

In our follow-up cauterization series, the ages ranged from 19 to 77 years (Table II).

TABLE II. AGES OF PATIENTS AT TIME OF CAUTERIZATION AND AT TIME OF FOLLOW-UP SURVEY: 2,224 WOMEN TREATED BY DEEP CAUTERIZATION OF CERVIX UTERI, 1914 TO 1939

AGE-GROUP YEAR	NUMBER IN EACH AGE-GROUP	
	AT OPERATION	AT LAST OBSERVATION
14	3	0
15-19	75	13
20-24	268	105
25-29	406	263
30-34	451	345
35-39	413	424
40-44	318	381
45-49	165	309
50-54	91	212
55-59	22	115
60-64	8	38
65-69	3	15
70-74	1	3
75-79	0	1
All ages	2,224	2,224
Average age at operation		34.6 years
Average age at last observation		40.1 years
Average period of observation		5.6 years

In the 10,000 series before the follow-up study was made, 2 patients were known to have developed cancer of the cervix (Cases 1 and 2). In the 31.4 per cent follow-up, or 3,143 patients, no additional cases of cancer of the cervix were found. Of the patients 73½ per cent were operated on by Dr. Huggins and myself by a technique that is quite constant. No case of cancer is known to have occurred in these patients. The 2 known cases of cancer developed in the remaining 26½ per cent operated upon by twenty-four other surgeons. Ten of these surgeons received their training with us, and the others are now practicing a similar technique, so that it is very unlikely that more than a small percentage of these cervices were cauterized less extensively than we practice. But there is some evidence that one of the two cancers which developed falls into this small percentage. This might indicate that superficial cauterization is less effective than deep cauterization as a prophylactic procedure. No such conclusion would be warranted, however, without a comparable series and follow-up of cervices superficially cauterized, for Holden[10] states that neither he nor Dickinson has seen a case of cancer develop after office cauterization.

DISCUSSION OF SURVEY

In order to determine the true prophylactic value of deep cauterization in this series, it is necessary to find out what should be the incidence of cancer in 10,000 gynecologic patients who have had no treatment of the cervix and who have been followed for years. No reliable figures of the incidence of cancer of the cervix in women in general are available.

But certain estimates can be made from isolated surveys and published

statistics. In the first examination of 1,200 women in general who volunteered for a program of periodic examination, Catherine Macfarlane[7] found 3 cases of unsuspected cancer of the cervix, an incidence of 0.25 per cent. An average of six similar figures from different sources would seem to place the incidence of cancer in women in general at approximately 0.19 per cent.

If this incidence were applied to our 10,000 series there would be 19 cases of cervical cancer at any one time.

Our patients were gynecologic cases, and in gynecologic cases and in those followed over a period of years, the incidence is much higher, for Meigs[8] cites a ten-year follow-up by Woolston of 1,014 patients who had had a repair of the cervix. It disclosed the fact that 1.87 per cent probably developed cancer of the cervix from six to twenty-nine years after operation. This corresponds quite well with the incidence in gynecologic cases in hospitals. An average of three such figures gives an incidence of 1.82 per cent. This incidence applied to the 10,000 series would be 182 cancers.

The true incidence would probably lie between these two figures, 19 cases for 10,000 women in general, and 182 cases in 10,000 gynecologic cases. Levin[9] who has done notable statistical work on cancer is more specific in his estimates. He approached the problem in a new and different manner, and by applying accurate and scientific statistical methods to our data, estimated the expected incidence of cancer in the various age groups. This is a very valuable contribution to statistical methods for similar surveys in the future. He writes as follows:

> Among 3,143 women followed for varying periods after deep cauterization of the cervix by Dr. Cashman and his associates, there were observed 79 deaths from all causes. In 2,224 of these patients, the average age at the time of cauterization was 34.6 years and the average age at the time of death or last observation was 40.1 years. The average period of observation was 5.6 years (Table II).
>
> The expected number of deaths from all causes and from uterine cancer in this group were calculated by applying to each age-group for the period of observation the mortality rates among females in Pittsburgh for the census year 1930 (Table III). It was found that during the period observed only 6 deaths from cancer of the uterus would be expected in the 3,143 patients, whereas two occurred.
>
> It is, therefore, at once clear that these patients have not been followed long enough to test adequately whether or not they will remain comparatively free from subsequent development of uterine cancer. This point may be amplified by citing the fact that if the entire group, 3,143, were observed from the time of cauterization until all had died, the number of deaths from uterine cancer which would be expected to occur is 79. The period of actual observation, however, was such that only 6 deaths might be expected. Even if we disregard the fact that only 55 per cent of the expected deaths from all causes were observed, the difference between 6 and 2 deaths in a sample of this size cannot be considered significant.

On the basis of this material I would, therefore, conclude first, that the number of patients followed and the average duration of the follow-up was too small to constitute a fair test of the value of cauterization of the cervix in preventing subsequent development of carcinoma; and, second, that as far as the facts obtained *in this survey* go, they do not indicate that cauterization has any prophylactic value. In view of the importance of settling this question, it is to be hoped that Dr. Cashman will continue his investigation by continued follow-up of these patients.

TABLE III. EXPECTED AND OBSERVED DEATHS FROM ALL CAUSES AND FROM CANCER OF THE UTERUS AMONG 3,143 WOMEN FOLLOWED FOR VARYING PERIODS AFTER DEEP CAUTERIZATION OF THE CERVIX

	NUMBER OF PATIENTS	DEATHS FROM ALL CAUSES			DEATHS FROM CANCER UTERUS		RATIO OBSERVED / EXPECTED	
		OBSERVED		EXPECTED†	OBSERVED	EXPECTED†	DEATHS FROM	
		NUMBER	PER CENT	NUMBER			ALL CAUSES	CANCER UTERUS
Age known	2,224	58	2.6	102	2	4	0.57	0.50
Age unknown	919	21	2.3	42*	0	2*	0.50	---
Total	3,143	79	2.5	144	2	6	0.55	0.33

*Deaths expected in group with age unknown on assumption of same experience as that in group with age known.

†Deaths expected on basis of age-specific mortality among all females, Pittsburgh, 1930.

Although no other cases of cancer were found in this survey it is evident from Levin's studies that the survey covered predominantly patients who were in an age group in which cancer of the cervix is not common, for the average age of the follow-up series was 40 years, and in our cancer of the cervix series, 69 per cent occurred in patients over forty years of age. It is stated that ten to fifteen years of chronic irritation seems to be necessary before cancer of the cervix develops, and our follow-up averaged only 5.6 years. This means that most of the patients in our follow-up cases were operated upon in the last five to fifteen years. This would be expected, as the longer the time interval after operation the more likely it is that the patient is lost through change of address, etc.

Levin feels that this study does not disprove the clinical impressions and statistical evidence that chronic cervicitis is a causative factor in cancer of the cervix and that the elimination of chronic cervicitis will prevent cancer. He found our incidence very low as compared to other statistics but that our follow-up study covered only to the lower limits of the age groups where the incidence of cancer rises rapidly. A few more years of observation of this group should give very definite information. He feels also that his estimates were based on women in general, while our series consists of women who came for gynecologic treatment and that due allowance should be made for this factor.

If the group that we contacted can be followed for another five or ten years, the question should be settled definitely. We intend to carry it on in our Department and with a more intensive effort to contact those patients who were operated upon more than five or ten years ago.

The recorded incidence of cancer of the stump is also higher than in women in general. Dr. Huggins and I have done 2,525 subtotal hysterectomies with cauterization of the cervix. They are included in the 10,000 series and information was obtained on 506 of them in the follow-up study. We know of no instance of cancer of the stump in this group. If Neilson's[3] estimate of approximately 1 per cent is correct, there should develop 25 cases in our hysterectomy series.

COMMENT

Perhaps there is no method of preventing cancer of the cervix 100 per cent, but in our personal series we have been unable to find a single case in spite of an honest effort at follow-up. A larger series of cases, or a longer period of time and a better follow-up may change that report. Even so, if it is shown that the incidence of cancer has been much reduced, the work has been worthwhile. It is much more satisfactory than the cure of an equal number of cancers of the cervix, for many of the cancer-cured cases are uncomfortable and unhappy; uncomfortable from undesirable radiation effects; and unhappy because of the dread of recurrence. Our interest has been in the prevention, rather than the cure of cancer of the cervix in the advanced stages in which it is usually seen today.

There were 25.4 per cent of the patients in our cancer series who had had pelvic operations, and one-half of them within five years before they reported with cancer. No prophylactic treatment of the cervix had been done, and the opportunity for the prevention of cancer had been lost.

The chief disadvantage of deep cauterization is the necessity for the irksome postoperative dilatations, but if the patient is completely relieved of cervicitis and if cancer is prevented, it is worth the effort. Before the advent of radium, the cautery was a valuable agent in the treatment of cancer of the cervix. It should be more effective before the onset of cancer.

In such a series, it may be that occasionally an incipient cancer, too small to be even suspected on gross examination, has been destroyed by the cauterization.

Prevention of cancer of the cervix, by any method that is effective, is advocated in this paper. Deep cauterization has been the method used in this series because it can be quickly done along with other operative procedures, and sections show that it is effective in eliminating cervicitis.

CONCLUSIONS

1. Chronic cervicitis seems to be a contributing factor in the causation of carcinoma of the cervix.

2. Cancer of the cervix is insidious in onset and because of the late stages in which it is seen today, prevention of cervicitis, prevention of cancer by adequate treatment of existing cervicitis, and early diagnosis by periodic examination of women over 25 years of age, offer the best solution of the problem.

3. In order to destroy infection in the cervix by cauterization it is often necessary to cauterize deeply and extensively.

4. Careful postoperative care is necessary to prevent stenosis of the cervical canal after deep cauterization.

5. As far as we know, deep cauterization of the cervix has been an effective method of preventing cancer in our series of 10,000 cases, for only 2 cases of cancer of the cervix are known to have occurred in this series.

6. A follow-up study was carried out but the average time interval after cauterization was only 5.6 years and the average age of the patient 40 years. The results therefore fail to show any very marked reduction in the incidence of cancer in the group followed, for by a new application of a statistical method to our series of 3,143 followed patients, Levin estimates the expected incidence as only 6 deaths from cancer of the uterus in the time observed. Two deaths are known to have occurred and one of these was from cancer of the cervix. A longer follow-up study will be necessary before definite information can be given.

7. Deep cauterization and subtotal hysterectomy has made total hysterectomy unnecessary for benign conditions of the uterus.

I wish to express appreciation to the members of the Gynecological and Obstetrical Staffs of the Elizabeth Steel Magee and St. Francis Hospitals, Pittsburgh, Pennsylvania, for their cooperation in permitting and aiding in the survey on their patients; to Dr. Mortimer Cohen, Dr. Albert Bruecken, Dr. John Frank, and Miss Anne Shiras for the pathologic sections, photomicrographs, color photography, and lantern slides; and Miss Theresa Mayer and Mrs. Betty Neeld for their seemingly endless work in trying to contact these patients and record the results in various ways.

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THE RATE OF ENTRANCE OF AMNIOTIC FLUID INTO THE PULMONARY ALVEOLI DURING FETAL RESPIRATION*

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THE present investigation is an attempt to determine the extent to which the respiratory movements of the fetus function to promote a tidal flow of fluid between the amniotic sac and the alveoli of the lungs.

The question as to whether or not the amniotic fluid normally enters the lungs during intrauterine life was raised long ago by Ahlfeld in connection with his observations of rhythmical excursions of the abdominal wall of women near term, which movements he described as evidence of respiratory excursions of the chest wall of the fetus. Ahlfeld expressed the view that amniotic fluid did not enter the fetal lungs.

A second type of evidence bearing upon this question has accumulated, namely, the finding of amniotic sac contents in the lungs of infants at autopsy.

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Farber and Sweet found cellular debris characteristic of amniotic fluid in 88 per cent of the lungs of infants which survived two hours to five weeks after birth in a series of 124 cases. More recently, Camerer found constituents of amniotic fluid in the lungs of all cases except three in a series of 212 autopsies which included 93 stillborn and 119 infants that died within one hour to one week after birth. Furthermore, extensive pneumonia in stillborn babies and those succumbing soon after birth has been noted with increasing frequency as microscopic examination of the lungs has been made (McGrath and Kuder, 1936; Chase, 1935; Warwick, 1934; Cruickshank, 1930; Hook and Katz, 1928; Johnson and Meyer, 1925; Browne, 1922; Slemons, 1915). For instance, Johnson and Meyer found evidence of pneumonia in 97 cases of a series of 500 consecutive autopsies at the Sloane Hospital, and in 68 of these it seemed probable that infection occurred before birth.

Additional evidence of the entrance of amniotic fluid into the lungs before birth has been obtained by x-ray of the fetus following injection of the amniotic fluid with thorotrast.

Observations have been made in women (Ehrhardt, 1938; Reifferscheid and Schmiemann, 1939) and in guinea pigs (Windle, 1939). Ehrhardt noted aspiration of amniotic fluid by a fetus of 20 cm. length or four to five months' development. Reifferscheid and Schmiemann reported similar results. Numerous sources of error inherent in the thorotrast method and resulting in failure to obtain x-ray evidence of its presence were pointed out by Ehrhardt in a careful study in women and laboratory animals.

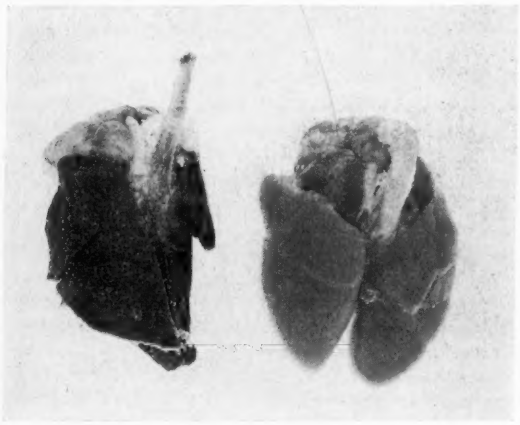
A new approach to the problem is afforded by the recent development of an experimental method which permits direct observation of fetuses showing rhythmical respiratory movements within the unopened uterus (Snyder and Rosenfeld, 1937). By the addition of foreign substance like carbon particles of India ink, the amniotic fluid may be readily stained and then traced in various parts of the respiratory passages. It is possible to see and count the intrauterine respiratory excursions. Thus, for the first time in fetuses under direct observation showing rhythmical breathing for many hours, one may determine whether or not fetal respiratory movements result in the entrance of amniotic fluid into the lungs. Evidence of the rate of exchange between the amniotic sac and the pulmonary alveoli is obtained by sacrifice of breathing fetuses at various intervals after injection of the amniotic sac.

METHOD AND MATERIAL

In a typical experiment a rabbit at full term, i.e., 32 days, was selected for observation. Inhibition of labor was assured by the induction of ovulation a week before term, i.e., at 25 days, by the injection of 100 rat units of extract of urine of pregnancy, antuitrin-S (Parke, Davis and Company). Inspection of the animal's abdomen showed localized rhythmical movements which were transmitted from fetuses at various sites where the uterus was in direct contact with the abdominal wall. The respiratory rate of various fetuses could readily be counted. In order to permit laparotomy and at the same time to avoid the effect upon the fetuses of a general anesthetic, the spinal cord was sectioned at the lumbar level. The uterus was exposed by laparotomy carried out beneath the surface of a large bath of Ringer's solution at 37° C. The fetal respiratory movements were easily observed directly through the thin uterine wall. The rate of the excursions was noted. In order to stain the amniotic fluid, 1 c.c. of 50 per cent India ink was introduced within the amniotic sac in the dorsal neck region between the ears. Discoloration of the entire sac was almost immediately evident. After intervals which ranged from one minute to many hours the trachea was closed by clamping the neck of the fetus. As a control, apneic fetuses of the same

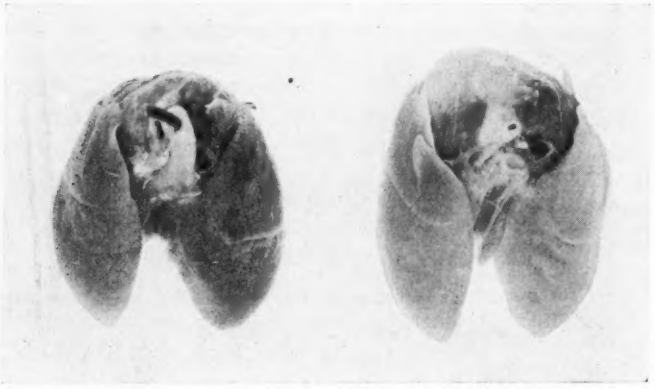
litter were observed following injection of India ink within the amniotic sac. Pentobarbital sodium was injected directly into the fetus for the suppression of respiratory movements.

The present observations are based upon 30 fetuses obtained from 10 rabbits at term. Seventeen fetuses were breathing at the time of injection of the amniotic sac while 13 were apneic.



A. *B.*

Fig. 1.—*A*, Lung of rabbit fetus breathing within the uterus obtained three minutes after injection of India ink into the amniotic fluid. *B*, Lung of apneic fetus obtained twenty minutes after injection of sac. In both fetuses 1 c.c. of India ink was introduced into the amniotic fluid. Entrance of stained fluid in *A* and the absence of it in *B* demonstrated that intrauterine respiratory movements result in the breathing of amniotic fluid.



A. *B.*

Fig. 2.—*A*, Lung of rabbit fetus breathing within the uterus obtained one minute after injection of India ink into the amniotic fluid. *B*, Lung of apneic fetus.

OBSERVATIONS

The entrance of blackened amniotic fluid into the lungs of fetuses which showed respiratory movements was regularly observed. In contrast, in apneic littermates the lungs failed to show carbon particles despite immersion of the fetuses in ink-stained fluid. It is evident that the intrauterine movements of the chest and diaphragm function to promote a tidal flow of fluid between the amniotic sac and the alveoli of the lungs. Evidence of the magnitude of the tidal exchange is afforded

by comparison of lungs which were obtained from fetuses at various intervals following injection of the amniotic sac with ink. Thus, in littermates which were breathing at the rate of 28 per minute, the trachea was clamped three minutes following injection of the amniotic sac of one fetus and one minute after similar injection of a second fetus. The extensive blackening of the lungs of the first one shows the rapidity of entrance of the dark-colored amniotic fluid into the fetal air passages (Fig. 1). In the second fetus much less carbon is to be seen although scattered black areas are clearly evident in the lungs even within one minute after staining of the amniotic fluid (Fig. 2). The findings are confirmed by microscopic examination. Carbon particles are found in the pulmonary alveoli and large air passages throughout the lungs.

Furthermore, in various fetuses of the same litter which were breathing at different rates, it was noted that the lungs were darker in those which showed the greater respiratory activity. For instance, in a fetus breathing at the rate of 96 per minute for five minutes after addition of 1 c.c. of ink to the amniotic fluid, the lungs were much darker than those of a littermate removed after sixteen minutes of breathing ink-stained fluid at the rate of 10 per minute.

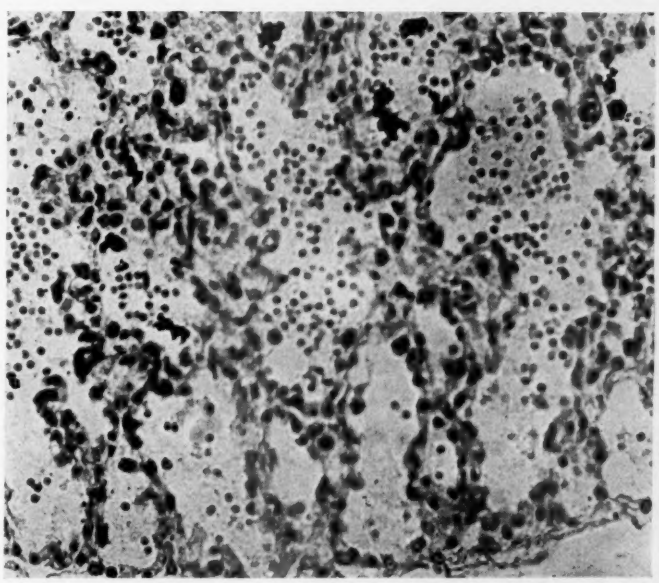


Fig. 3.—Lung of rabbit fetus stillborn following contamination of the amniotic fluid with blood. The pulmonary alveoli contain blood cells.

In Fig. 3 is shown the lung of a rabbit which died undelivered at full term. At autopsy the amniotic fluid was conspicuously stained with blood. Microscopic examination of the lungs revealed the presence of blood uniformly distributed throughout both lungs. Contamination of the amniotic fluid was associated with accidental hemorrhage of the placenta.

SUMMARY

From the foregoing experiments, it is evident that ink-stained amniotic fluid promptly enters the pulmonary alveoli of breathing fetuses but is

not found in lungs of apneic ones. In the brief period of a minute of intrauterine respiratory activity, there is a striking flow into the pulmonary alveoli of the fluid in which the fetus is immersed.

The presence of amniotic fluid in the lungs and its tidal flow during normal fetal life afford a basis for tracing the origin of damage to the future air passages.

In so far as there is obscurity regarding the mechanism whereby extensive injury of the lungs occurs before birth, even resulting in intrauterine death associated with pneumonia, it is apparent that the present findings provide a new link in the chain of evidence, by which intrauterine pneumonia is connected with abnormality of the amniotic fluid.

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DISCUSSION

DR. W. F. WINDLE.—We have confirmed Dr. Snyder's factual observations. However, I must disagree with some of the interpretations he has placed upon them.

The physiology of respiration in the fetus in utero is not so greatly different from that of the newborn infant or even of the adult as it might seem. If it is to be understood clearly it should be viewed in the light of at least three fundamental concepts.

I. A respiratory center develops in the embryo, reaching a functional state as early as the twelfth week in man. This center seems to be inactive but can be activated by (a) afferent nervous impulses discharging into it, (b) by the chemical agent, carbon dioxide, acting upon it directly, or (c) by anoxial enhancement of its excitability (lowering its threshold). It is doubtful if the fetal respiratory mechanism actually functions in the strictly normal course of intrauterine existence; its threshold is very high. The fetal respiratory mechanism is a dormant system charged with potentialities, long in advance of the time it can be of any use.

II. The mammalian fetus does not thrive on venous blood, as commonly taught. It receives well-oxygenated blood from the placenta, and this blood reaches the fetal brain without great loss of oxygen. It has been proved in the sheep that the umbilical vein blood is 90 to 95 per cent saturated throughout a fair portion of the gestation period. The fetal carotid artery blood is as much as 88 per cent saturated with oxygen. In the last days of gestation the values decline somewhat, and a physiologic partial anoxemia becomes established. This is by no means an asphyxia. Some confirmatory data are available for man.

III. The fetus in utero is hypotonic if not actually atonic. It appears to lack a well-developed mechanism to return its blood to the heart. The uterine musculature substitutes for this lack of tonus, and rhythmical prelabor uterine activity assists in returning blood to the fetal heart. In some species of animals, notably the cat, each uterine contraction sends a freshet of well-oxygenated blood to the fetus. In late pregnancy each uterine relaxation allows a partial anoxemia

to manifest itself in the fetal brain, and fetal activity ensues in consequence, only to subside again with the succeeding uterine contraction.

Keeping these concepts in mind let us examine the question of fetal respiratory movements and aspiration of amniotic fluid. Under experimental conditions which interfere in any way with normal oxygenation of the fetal brain, it is very easy to obtain rhythmical movements which are not present normally in fetuses. In Dr. Snyder's experiments the normal uterine motility had been inhibited hormonally. This may have impaired the mechanism which returns blood to the fetal heart and may have allowed an anoxemia to be set up in the fetal brain. Anoxemia affects the fetal respiratory center, lowering its threshold to a point which can be reached by the usual stimulatory agent, carbon dioxide. Had Dr. Snyder obtained blood gas analyses in his specimens, I am confident he would have found very little oxygen in the fetal blood. We have done that in the cat and I can say that fetal quiescence and apnea (true physiologic apnea, not asphyxial apnea) are associated with values in excess of 50 per cent saturation, rapid rhythms of respiratory movements with values between about 25 and 50 per cent saturation, and slow dyspneic rhythms with values well below 25 per cent saturation with oxygen. In fact the gasping movements persist when the fetal blood contains less than one-half a volume of oxygen per cent.

In late prenatal life when the placenta may be said to have undergone some physiologic deterioration, the rapidly growing fetus is hard pressed to get enough oxygen. With each uterine relaxation, the fetus becomes active and may even exhibit some rapid respiratory rhythms. Such movements may occur occasionally in the human being near term, but their incidence is certainly not great, and it is not proved that they occur in all.

Even if these fetal respiratory rhythms are truly of normal occurrence, which may still be questioned, do they result in aspiration of the amniotic fluid? In the absence of muscle tonus, a negative intrathoracic pressure does not manifest itself. The normal fetus is hypotonic if not actually atonic.

We have proved that aspiration of amniotic fluid can occur in fetal guinea pigs, but only under asphyxial conditions. Thorotrast was introduced into the amniotic sacs of 27 fetuses without anesthetizing the pregnant animals; normal physiologic conditions were maintained. Roentgenograms taken within a few minutes, a few hours, and at daily intervals until birth revealed that this material entered the fetal lungs in none of these specimens. However, in another series of experiments similarly performed but in which the mother guinea pigs were later subjected to anoxemia or asphyxia, the fetuses executed respiratory movements and 9 out of 25 aspirated the thorotrast. Asphyxia at birth resulted in aspiration in three other animals.

These experiments lead us to believe that aspiration of amniotic fluid is not a normal function. Some investigators experimenting with the human being and the monkey have also confirmed these studies in the guinea pig. Other investigators using the human subject have observed aspiration of amniotic fluid, but there is no indication that physiologic conditions were maintained in the latter experiments.

In conclusion, let me emphasize the need of critical evaluation of experimental conditions in studies in physiology of the fetus. When this is done, one may well question whether all human fetuses exercise their respiratory mechanism in utero near term. Even those that do so need not be assumed to aspirate the fluid.

DR. JOSEPH L. BAER.—The soundness of Dr. Snyder's deductions was challenged by Dr. Windle. In this connection it occurred to me that it is common knowledge to all who are familiar with fetal heart tones in labor that there is a relationship between heart rate and uterine contractions. It is common knowledge that if we want a true evaluation of the fetal heart rate we instruct the supervisor or the intern not to listen immediately at the end of the contraction but to wait a moment or two. With the onset of a contraction, the fetal heart rate drops decidedly, then after the uterus relaxes, there is an equally rapid acceleration of the heart rate, somewhat above the normal rate for that fetus, and then it steps down to its normal rate until the next contraction occurs. Possibly that observation fits in with Dr. Windle's comments. Perhaps the fetal heart slows down because it gets adequate oxygenation from the blood of the placenta at the time

of the contraction, the placenta being more or less compressed, and then as the uterus relaxes the heart becomes more rapid. I would like to have Dr. Windle tell us if the heart rate slows with each contraction because of excess blood supply and oxygen or because of asphyxia.

Another thought is that, assuming intrauterine respiration, the fetus at birth carries with it from the uterine cavity a certain quantity of amniotic fluid in each of the alveoli even though the alveoli after birth are somewhat distended by air added to their content. Unless that residual amniotic fluid is rapidly absorbed by the epithelium of the alveoli, it should make its appearance from the lungs and out through the mouth and nose of the newborn infant. We do see newborn infants whose pharynx and trachea are filled with amniotic fluid, blood, meconium, etc., but the infant who cries lustily at birth does not have the sound of a child whose lungs are partly filled with amniotic fluid.

DR. SNYDER (closing).—Regarding Dr. Windle's anatomic observations in guinea pigs, it is interesting that aspiration of thorotrast was revealed by x-ray in certain fetuses but not in all cases. In this connection, Ehrhardt pointed out in his last paper (1939) that the presence of thorotrast in amniotic fluid or in the gastrointestinal tract may escape detection by x-ray. Thus, in mice drinking a diluted solution of thorotrast for several days, no x-ray evidence of its presence was obtained; however, after an additional period of days a definite shadow in the gastrointestinal tract was obtained, indicating a separation of thorium and the diluting medium probably by the intestinal epithelium. Similarly after injection of the amniotic fluid with thorotrast, various intervals, for example seventy-two hours, elapsed before a shadow appeared in the respiratory tract. Ehrhardt concluded that the mechanism for separation or concentration of thorium was even less effective in the respiratory passages than in the intestinal tract.

The various other problems which were raised require separate answers. Regarding such a question, for example, as the nature of the chemical regulation of fetal respiration, it would seem that Dr. Windle's conclusions do not always take into account all of the available data.

In connection with Dr. Baer's point concerning the absorption of fluid from the lungs, it is interesting to recall the structure of the pulmonary alveoli. Bloom's investigations have shown that it is difficult to demonstrate a continuous epithelial lining, the capillaries appearing to be uncovered. The morphologic barrier to exchange between the lumen of the alveolus and the blood stream is thus reduced to a minimum.

Trussell, Ray E.: Hypersensitivity as a Factor in Chronic Monilia Vaginitis, J. Iowa M. Soc. **29:** 485, 1939.

It is now well established that a marked growth of yeastlike fungi in the vagina, particularly in pregnant and diabetic women, may produce acute vaginitis. Such patients are usually treated satisfactorily with gentian violet, but even if untreated, some experience spontaneous cure with termination of the pregnancy or after control of the diabetes.

In contrast to this type of severe vaginitis which is encountered only occasionally, it is common to see women who complain only of vaginal and vulval itching and in whom cultures reveal no commonly recognized vaginal pathogens except a few "monilia." Such infections are at times refractory to the usual fungicides and the itching and low grade inflammation persist.

Recently it has been suggested that certain of these women are hypersensitive to the fungi and that the itching and mild inflammation are manifestations of a local allergic reaction.

Ray E. Trussell tested 200 pregnant women and found that a large percentage of adult women are skin sensitive to commercial oidiomycin. It would appear that the use of this fungus extract for skin tests would be of limited value in indicating suitable cases for desensitization of patients with chronic monilia vaginitis on the theory that the condition may be on an allergic basis unless focal flare-ups or skin reactions stronger than normal can be shown to occur consistently.

J. P. GREENHILL.

UNEXPECTED POST-PARTUM HYPERTENSION

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FOR the purposes of this paper, "unexpected post-partum hypertension" is defined as an elevation of the blood pressure above physiologic limits as found by us at the routine six weeks' post-partum examination. Elevations above 140 systolic and 90 diastolic are considered abnormal. To eliminate all "toxemias of pregnancy" and cardiovascular renal disease, it is also required that the prenatal and immediate post-partum pressure be normal.

Elsewhere, one of us (H. M.)[1] has reported 23 cases of post-partum hypertension. Since that time, we have observed 28 additional cases which have confirmed our original observations and brought to light some new and interesting data. Our routine has been simple: Cases of post-partum hypertension were carefully studied in the obstetric clinic and then referred to various departments of the outpatient clinic for special study. In most instances medical examination was followed by ophthalmoscopic examination, x-ray, electrocardiogram, blood, urine, and kidney function studies.

The salient features of this condition may be noted upon reference to the tables of data. In Table I it may be noted that most of the patients are multiparas. They were for the most part observed during pregnancy long enough to obtain adequate control data on the blood pressure. The post-partum hypertension usually lasts six to seventeen weeks. The attainment of the maximum pressure may not occur until the sixteenth post-partum week, though usually the maximum is seen about the sixth post-partum week (Table I).

TABLE I

I. Age	18-20 2 cases						20-30 15 cases					30-40 11 cases	
II. Gravida	i	ii	iii	v	vi	vii	viii	ix	x	xi	xiii		
Cases	4	8	2	3	1	3	1	2	2	1	1		
III. Enrolled	First Trimester 5						Second Trimester 19					Third Trimester 4	
IV. Number of prenatal visits	3-5						5-10					over 10	
Cases	4						6					18	

V. Number of pregnancies with post-partum rise	40
Unknown duration of post-partum rise	21
Known duration of post-partum hypertension	19
Six to seventeen weeks post partum	15
Seventeen to twenty-two weeks post partum	2
Forty-six weeks post partum	1
Forty-nine weeks post partum	1

VI. Maximum post-partum blood pressure							
Weeks post partum	6	7	8	8	10	11	16
Cases	20	3	3	1	4	1	1

In view of the fact that we have been able to find post-partum hypertension only in the negress, we calculated the average pressure for normal white and colored patients during the prenatal and post-partum periods. One hundred case records of white and colored patients were studied in compiling the data recorded in Table II. The average prenatal pressure was also obtained for the patients in this series who showed the unexpected post-partum rise. Two facts are apparent. First, while prenatal pressures of normal white and colored patients are about the same, the normal colored patients tend to show a higher post-partum rise. Second, normal colored patients show a somewhat lower prenatal pressure than do those exhibiting the unexpected post-partum rise (Table II).

TABLE II. AVERAGE PRENATAL AND POST-PARTUM BLOOD PRESSURE WITH STANDARD DEVIATION

I. Normal patients	
a. Colored	
(a) Prenatal	
1. Systolic	109.48 ± 7.39
2. Diastolic	66.55 ± 6.7
(b) Post partum	
1. Systolic	120.8 ± 11.1
2. Diastolic	77.38 ± 7.9
b. White	
(a) Prenatal	
1. Systolic	110.1 ± 6.5
2. Diastolic	69.0 ± 5.1
(b) Post partum	
1. Systolic	114.15 ± 8.1
2. Diastolic	73.9 ± 7.3
II. Patients with post-partum hypertension	
(a) Prenatal	
1. Systolic	116.3 ± 6.0
2. Diastolic	73.38 ± 4.3

Tables III to X represent data from selected cases of post-partum hypertension designed to illustrate the salient features of this syndrome. Table III shows that the maximum pressure may occur as early as six weeks post partum, and Table IV reveals that the maximum rise may not occur until much later. This post-partum rise does return to normal and has been observed to remain there as indicated in Table V. While the duration of this hypertension is usually about ten weeks, it may last twenty-five weeks or more (Table VI). The case reported in Table VII supplies a number of interesting observations. The patient's pressure during pregnancy and labor was somewhat lower than it was a year previously. At no time during or after pregnancy was she aware of any illness despite the fact that she exhibited a marked unexpected post-partum rise lasting at least forty-two weeks. Observed in

TABLE III

152-491, aged 20, primipara, second trimester, 8 prenatal visits	
Blood pressure during pregnancy	112-120
	70-86
Blood pressure during labor	130-136
	70-80
Immediately post partum	135/85
Six weeks post partum	160/120
Twelve weeks post partum	150/105
Thirteen weeks post partum	130/85
Fifty-one weeks	118/88
Blood picture, chemistry, urinalysis, eyegrounds, chest plate, and physical examination all negative.	

TABLE IV

114-383, aged 29, gravida v, first trimester, 19 prenatal visits (1937)	
Blood pressure during pregnancy	108-124
	70-80
Blood pressure during labor	132/84
Blood pressure 6 weeks post partum	146/94
Blood pressure 10 weeks post partum	154/100
Blood pressure 11 weeks post partum	170/110
Blood pressure 12 weeks post partum	160/110
Blood pressure 13 weeks post partum	118/96
Blood pressure 14 weeks post partum	130/95
Blood pressure 15 weeks post partum	130/88
Blood pressure 16 weeks post partum	115/80
Blood pressure 18 weeks post partum	130/85
Blood pressure 20 weeks post partum	130/85
Blood pressure 79 weeks post partum	122/80
Physical examination and laboratory test entirely negative.	

TABLE V

14942, aged 38, gravida ii, second trimester, 13 prenatal visits	
Blood pressure during pregnancy	90-114
	60-72
Blood pressure six weeks post partum	192/110
Seven weeks post partum	190/110
Thirteen weeks post partum	152/110
Fourteen weeks post partum	122/80
One hundred twenty-four weeks post partum	116/80
One hundred thirty-four weeks post partum	138/80
One hundred thirty-six weeks post partum	130/80
Wassermann, Fishberg, urinalysis, and physical examination negative.	

the post-partum period, a diagnosis of arteriosclerosis of the retinal vessels and hypertensive vascular disease was made.

Table VIII illustrates that post-partum hypertension can and does recur with succeeding pregnancies and that a repetition of the syndromes may be less severe than the preceding one. This speaks for a functional disorder rather than an organic disease. As a matter of fact, the post-partum rise may be entirely absent in subsequent pregnancies as shown in Table IX. In Table X it can be seen that the unexpected rise occurs in 3 successive pregnancies after a normal post-partum blood pressure in the first pregnancy.

TABLE VI

43574, aged 32, gravida x, second trimester, 5 prenatal visits	
Blood pressure during pregnancy	115-148 / 70-84
Blood pressure six weeks post partum	170/105
Blood pressure seven weeks post partum	160/100
Twenty-four weeks post partum	154/94
Twenty-five weeks post partum	160/100
Forty-six weeks post partum	120/90
Seventy-five weeks post partum	120/90
Four months prior to pregnancy the blood pressure was 142/96.	
Laboratory and physical examinations negative.	

TABLE VII

87377, aged 32, gravida viii, second trimester, 19 prenatal visits	
Blood pressure during pregnancy	120-134 / 68-84
Blood pressure during labor	108-118 / 68-88
Blood pressure six weeks post partum	148/110
Nine weeks post partum	200/130
Twenty weeks post partum	220/120
Twenty-eight weeks post partum	160/100
Thirty-six weeks post partum	180/115
Thirty-eight weeks post partum	164/94
Forty-two weeks post partum	156/100
One year before the onset of pregnancy the blood pressure was 140-154/80-88.	
Blood picture, urinalysis, Wassermann, chest plate, and basal metabolism negative.	
Eye grounds, marked arteriosclerosis.	
Medical diagnosis: hypertensive vascular disease.	

TABLE VIII

110-492, aged 28, gravida v, first trimester, 12 prenatal visits (1934)	
Blood pressure during pregnancy	100-122 / 60-78
Blood pressure six weeks post partum	168/120
Blood pressure eight weeks post partum	126/88
Twelve weeks post partum	120/90
Sixteen weeks post partum	124/92
(1936-37), aged 31, gravida vi, first trimester, 12 prenatal visits	
Blood pressure during pregnancy	100-118 / 60-80
Blood pressure during labor	130/96
Blood pressure six weeks post partum	146/100
Seven weeks post partum	140/105
Thirteen weeks post partum	138/90
Twenty-six weeks post partum	136/94
Thirty-seven weeks post partum	136/96
Laboratory and physical examination negative.	

Certain facts not recorded in the tables are worthy of comment. Upon survey of the literature, it was found that "unexpected post-partum hypertension" has been recorded on only two occasions.[1, 2] Stout found

TABLE IX

90419 The blood pressure during three pregnancies from 1928 to 1933 never exceeded 128/80, an average of 100 to 116.	
1935, aged 27, gravida iv, second trimester, 14 prenatal visits	
Blood pressure during pregnancy	112-136 / 70-84
Blood pressure six weeks post partum	180/110
Blood pressure ten weeks post partum	172/114
Blood pressure fourteen weeks post partum	192/112
Blood pressure eighteen weeks post partum	180/120
1937, aged 29, gravida v, second trimester, 14 prenatal visits	
Blood pressure during pregnancy	110-132 / 70-86
Blood pressure six weeks post partum	120/78
Blood pressure ten weeks post partum	120/86
Blood pressure one year post partum	126/88

TABLE X

136-490, aged 28, gravida i, third trimester, 5 prenatal visits (1934-35)	
Blood pressure during pregnancy	122-140 / 70-80
Blood pressure during labor	124-138 / 80-94
Blood pressure six weeks post partum	120/72
(1936) Aged 29, gravida ii, second trimester, 15 prenatal visits	
Blood pressure during pregnancy	108-130 / 60-84
Blood pressure during labor	122-128 / 70-84
Blood pressure six weeks post partum	148/98
Blood pressure seven weeks post partum	144/96
Blood pressure eleven weeks post partum	150/80
Laboratory and physical examination negative.	
(1937-38) Aged 31, gravida iii, first trimester, 22 prenatal visits	
Blood pressure during pregnancy	112-134 / 58-78
Blood pressure during labor	110-122 / 78-84
Immediately post partum	126/80
Six weeks post partum	160/105
Ten weeks post partum	130/95
Laboratory and physical examinations negative.	
(1938-39) Aged 32 gravida iv, second trimester, 16 prenatal visits	
Blood pressure during pregnancy	112-140 / 60-80
Blood pressure during labor	130-144 / 84-100
Immediately post partum	126/80
Six weeks post partum	140/100
Laboratory and physical examinations negative.	

that it occurs in white as well as colored patients; we have found it only in colored patients.

When these patients were observed in the medical clinic, a diagnosis of hypertensive vascular disease seemed warranted in all instances, although only two patients in the entire series showed any vascular damage and that was limited to the eye grounds. The seeming self-limitation

of the syndrome was significant. In no other case was a diagnosis suggested. The possibility of confusing "unexpected post-partum hypertension" and hypertensive vascular disease (essential hypertension) is a real one and the guarded prognosis of the latter given to the post-partum patient is entirely unwarranted.

We have as yet failed to observe congestive heart failure in any case of post-partum hypertension. The possible relationship of this syndrome to the curious post-partum congestive heart failure reported[3-5] is at present quite obscure.

SUMMARY

1. "Unexpected post-partum hypertension," coined term, is an idiopathic syndrome, relatively unstudied, and found by us only in the colored race.

2. The findings in 51 cases are summarized in this report.

3. Most of the patients are multiparas.

4. Practically all of the patients were observed during the prenatal period for an adequate time period to allow for evaluation of the post-partum blood pressure.

5. The duration of the post-partum rise is about six to seventeen weeks. It is self-limited.

6. The maximum pressure while usually observed six weeks' post partum may be as late as 16 weeks post partum.

7. The average normal colored patient shows a slightly higher post-partum pressure than does the average normal white patient. The average normal colored patient shows a lower prenatal pressure than does the colored patient who develops "unexpected post-partum hypertension."

8. The syndrome may or may not be present at subsequent pregnancies and if so, may be more or less severe than the previous occurrence.

9. No relationship of this syndrome to post-partum heart failure (idiopathic) has been apparent.

10. No etiologic factor is evident; there is some suggestion that it is purely functional.

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STUDIES IN PELVIC IONTOPHORESIS*

I. Iontophoresis in the Treatment of Pelvic Infections With a Report of 58 Cases

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PELVIC infections are very common. Approximately 500 cases a year in the wards at Kings County Hospital constitute our major problem. Radical operations are clearly contraindicated in young women and, in our experience, anything less is likely to be unsatisfactory. The clinical course of the infection depends, above all, upon its etiology and pathology. Mixed forms, largely due to gonorrhea and postabortive or puerperal infection, are common. In the majority of cases there have been frequent exacerbations. Actual resolution of large masses not infrequently occurs and symptoms tend to improve or subside with hospitalization. Improvement is so consistent as a matter of fact, that we believe that exacerbation follows re-infection, and that relief of symptoms is due to removal from the dangers of coitus, not bed rest alone. Operation has been performed for drainage of ovarian abscess, intraperitoneal abscess, whether abdominal or pelvic, and for relief of prolonged menorrhagia, severe dyspareunia, and disability of long standing. Our experience with conservative or nonoperative treatment has been discouraging. Foreign protein, repeated transfusions, and various forms of heat therapy have been unsatisfactory.

In August, 1940, we[1] reported our results with sulfanilamide in 74 cases of severe pelvic infection, concluding that this therapy should be used only in those acute cases in which the gonococcus or streptococcus was the infective agent. We observed no notable diminution in the size of pelvic masses, tuboovarian or otherwise. Cellulitic lesions did not respond at all. Sulfathiazole is now being given a trial.

Following the reports of Jacoby[2, 3] on the rapid absorption of exudates by pelvic iontophoresis of acetyl-beta-methylcholine chloride (mecholyl chloride), we selected patients for this form of therapy. In subsequent papers we shall report upon the physiology of iontophoresis, and its use in fibroid tumors of the uterus with associated pelvic inflammation.

Iontophoresis is the act of driving positively or negatively charged ions into the tissues underlying the skin or mucous membranes by means of a galvanic or direct current. The intent with the use of mecholyl chloride is to produce local hyperemia,[4] said to be more intense and more prolonged than that initiated by heat therapy. The local effect is clearly vasodilatation, probably of the capillary bed, with fall in blood pressure, increase in the pulse rate, salivation, lacrimation, flushing, and sweating. This systemic response follows oral or subcutaneous administration as well.

*Read at a meeting of the Brooklyn Gynecological Society, October 4, 1940.

TECHNIQUE OF THERAPY

The following articles are necessary for a treatment:

1. An apparatus capable of delivering a direct current of 15 to 20 milliamperes (Fig. 1).
2. A vaginal electrode consisting of an insulated metal rod terminating at one end in a small mobile crosspiece.
3. 20 c.c. of ½ or 1 per cent mecholyl chloride and enough gauze for saturation.
4. An abdominal galvanic pad 6 by 8 inches.
5. A bivalve vaginal speculum, sponge stick, and sponges.

The procedure follows:

The pad is first soaked in warm tap water; if not wet enough, it may be difficult to raise the milliamperage. With the patient in the lithotomy position, the cervix is exposed and the vaginal vault wiped dry, so that the drug may make close contact. The gauze saturated with mecholyl chloride is then wrapped about the vaginal end of the electrode, held firmly against the vaginal vault with the crosspiece at right angles to the shaft, and the speculum carefully withdrawn. The

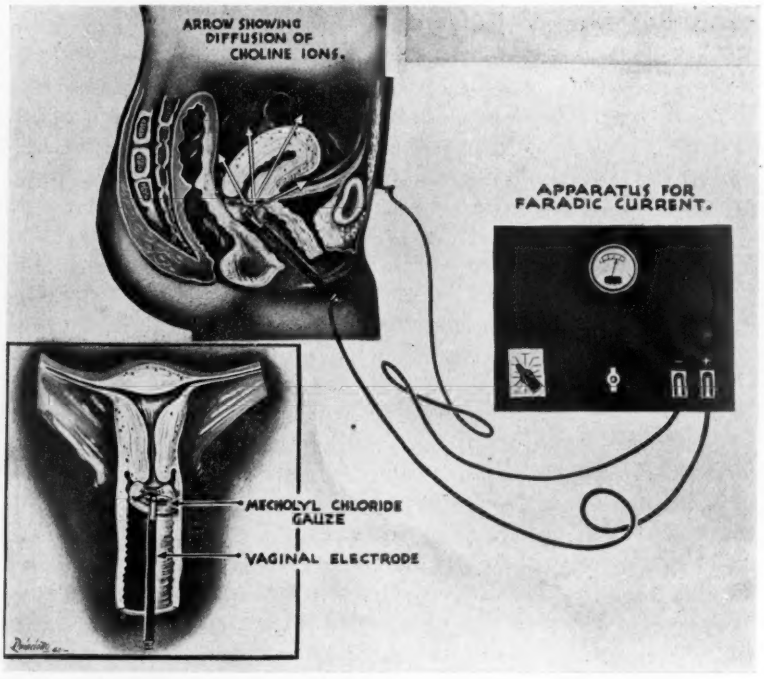

Fig. 1.

electrode is then attached to the positive pole, the current turned on, and increased slowly to 15 or 20 milliamperes. The patient generally experiences a slight local sensation of shock if the current is increased too quickly. The abdominal pad is held firmly against the skin by a binder or sandbags. A sensation of pricking, burning, or sticking, due to failure of the pad to make sufficient contact, may be eliminated by having the patient press it down with her hands. The treatment should last twenty minutes, when the current should be decreased slowly, or the patient may again experience slight local shocking.

Increase in the pulse rate, flushing, sweating, lacrimation, and salivation should be looked for, so as to be certain that absorption of sufficiently active solution of the drug is taking place. Treatments should be given every other day for two to four weeks, depending upon response to therapy.

PERSONAL OBSERVATIONS

During the past two and one-half years, 37 patients with tuboovarian and 21 patients with cellulitic infection were selected for treatment; 43 were from the Kings County Hospital and 15 from the service of Dr. Alfred C. Beck at the Long Island College Hospital.*

Diagnosis and the extent of the pathology were based principally on the pelvic findings of unilateral or bilateral tender inflammatory masses; in 12 cases these masses were so large as to be felt abdominally. In 21 cases there was evidence of previous severe infection, and in 11 cases a history of operative procedures including salpingectomy, colpotomy, intratubal injection of turpentine, and drainage of a Bartholin abscess. Pain and menstrual disturbances were common. In 15 cases abscess or pelvic peritonitis or both were present. In 13 cases of cellulitis, the exudate almost filled the pelvis, rising higher in 7 cases and to the iliac crest in 4. Three or more treatments with an average of 6 were given to 42 patients.

In the majority of cases, the patient had failed to respond to some form of therapy, and in 13 cases repeated blood transfusions and sulfanilamide therapy had been ineffective. In 27 cases, more than one week without clinical improvement had elapsed. This is a fair test, yet we realize that even a much longer period is open to question.

Occasionally, marked relief of pain, out of proportion to other evidence of clinical improvement, was noted. We have, however, based our opinion as to the value of therapy on objective response alone. Relief of pelvic pain was observed in 32 of the 42 patients who were treated adequately, and in 12 of the 16 patients receiving less than three treatments. One patient died of a postoperative cardiac complication one month after iontophoresis therapy had been finished. Decrease in size or disappearance of inflammatory masses or tenderness, normal levels of the leucocyte count and sedimentation time, and increased mobility of the pelvic viscera are excellent signs of improvement. In the case of tuboovarian disease, satisfactory change in the sedimentation time is good evidence of subsidence of infection. In this group of 37 patients, 24 received adequate treatment; in 14 of these, marked reduction in size of adnexal masses was observed.

In cellulitic infections the exudate is more readily observed. In 2 cases iontophoresis was given to patients thought to have deep parametrial abscesses in the hope of making incision and drainage easier. Resolution followed. When the exudate was small and of long standing, improvement as a rule was not remarkable.

Four cases have been selected to illustrate apparently good results.

CASE 1.—A. G., aged 39 years, para iv, was admitted on July 8, 1940, complaining of lower abdominal pain for thirteen days. Temperature was 100° F., sedimentation time twenty minutes for 18 mm., and the leucocyte count 12,950 with 87 per cent polymorphonuclears. The lower abdomen was very tender, and both adnexa were enlarged, cystic, and tender. After two weeks in bed, repeated blood transfusions, and full sulfanilamide therapy, the sedimentation time remained unchanged.

After 11 iontophoresis treatments, the sedimentation time became eighty-five minutes. At laparotomy on August 8, the left tube and ovary were found grossly normal, and the right tube and ovary moderately thickened and adherent to each other. Pathologic examination of the right tube and ovary showed minimal evidence of infection (Fig. 2).

CASE 2.—H. K., aged 18 years, was admitted on Jan. 15, 1938, with a history of pain in the right lower quadrant of the abdomen for three weeks. Temperature was 103° F., sedimentation time 25 minutes for 18 mm., and the leucocyte count 20,000 with 85 per cent polymorphonuclears. The lower abdomen was tender and spastic with peritoneal rebound pain. A diagnosis of pelvic peritonitis and cellulitis was made, and the patient received repeated blood transfusions and two courses

*We are indebted to Dr. Wm. A. Jewett, Dr. Harvey B. Matthews, and Dr. George W. Phelan for these cases.

of sulfanilamide therapy, totaling 725 gr. No improvement occurred during the next two months, with the temperature frequently going above 102° F., and the pelvic exudate spreading to the iliac crest.

Nine treatments were given between March 19 and April 8. On April 21 reduction in the size of the exudate was noted, and by April 30 the patient was practically symptom free and the residual mass was about one-third its original size. Her temperature became normal on April 11 and remained so until a slight elevation which preceded her unauthorized discharge from the hospital on May 11 (Fig. 3).

CASE 3.—A. M., an 18-year-old white primipara, delivered spontaneously at term on Sept. 2, 1939. She developed severe puerperal infection, and on the fifth postpartum day showed a mass in the right lower quadrant and spreading peritonitis with the temperature reaching 104.3° F. She was treated with sulfanilamide and numerous blood transfusions. She improved markedly and was discharged on September 28, with a small mass still present in the pelvis.

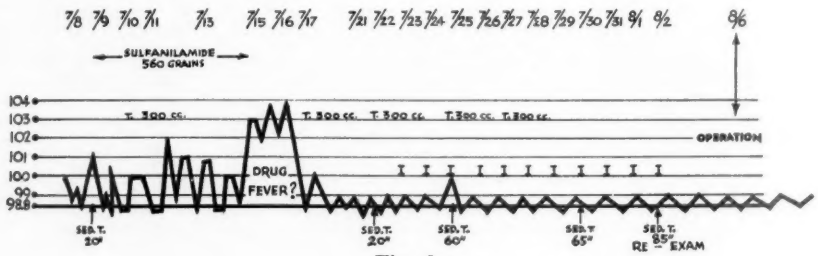

Fig. 2.

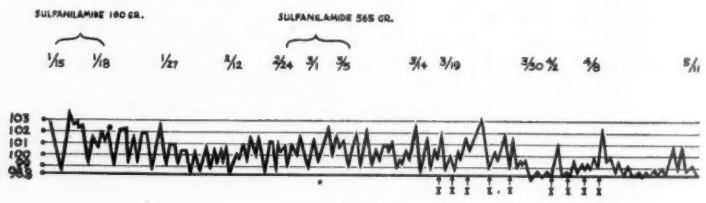

Fig. 3.

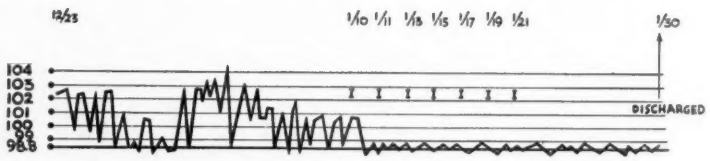

Fig. 4.

She was readmitted on December 23, complaining of intermittant vaginal bleeding and severe lower abdominal pain. Examination revealed an inflammatory exudate filling the right side of the pelvis and cul-de-sac, and rising to the crest of the ilium. The leucocyte count was 16,000 with 84 per cent polymorphonuclears, and the sedimentation time 40 minutes for 18 mm. On January 3, after a septic course with the temperature frequently rising above 102° F. and occasionally to 103° F., examination revealed deep fluctuation, and iontophoresis was begun. Subjective improvement was noted after the first treatment. Marked resolution of the mass followed, making operation unnecessary. Seven treatments in all were given. She was discharged from the hospital on January 30 with a small mass still present.

CASE 4.—B. L., aged 28 years, was admitted on Feb. 1, 1938, with pelvic cellulitis which followed two dilatations of the cervix for sterility. She improved but little on chemotherapy, and was discharged February 28. On March 31 she was

readmitted with a large cellulitic exudate which extended to the crests of both ilia. Temperature reached 103° F. She was treated by bed rest and repeated blood transfusions for a month without appreciable improvement.

From April 3 to June 4, 9 iontophoresis treatments were given. The first treatment relieved the pain which had persisted for a few months, and by May 30, after 6 treatments, she felt entirely well. When discharged on June 19, only a small mass remained. On follow-up examination on Oct. 31, 1938, small bilateral mobile, nontender, tuboovarian masses were noted. One year later she was well, and no masses or exudates could be felt on pelvic examination (Fig. 4).

DISCUSSION

The common symptoms of systemic reaction were observed, yet all were not present in every case. In addition, dizziness, frontal headache, dryness of the mouth and throat, palpitation, trembling, chilly sensations and pain in the lower abdomen, and vagina were rarely observed. Though vasomotor collapse is said to occur, we have not seen it, yet one patient did experience tachycardia and marked difficulty in breathing which improved at once when treatment was discontinued. One galvanic burn of the skin, in the shape of multiple small superficial ulcers, was observed; it subsequently healed. These burns are probably caused by electrolytic changes, and not by generation of heat or sparking beneath the pad. They may be due, of course, to electrode metal touching the skin, insufficient thickness of the pad, or skin defects.[5]

In 4 cases treatment appeared to aggravate the lesion. Failure of subjective improvement generally indicates a poor prognosis for therapy, though we have seen increased activity of the infection followed by resolution. In 4 cases a slight rise in temperature during the twenty-four hours following treatment was noted.

On the basis of objective findings alone, we have classified our results in 42 patients who received adequate therapy, since it is our opinion that less than three treatments with iontophoresis is inadequate therapy.

Group I: Good Result. Those who improved on iontophoresis after failure of supportive therapy, blood transfusion, and chemotherapy, and those who showed striking improvement, though the control period had been short.

Group II: Doubtful result. When response had been good, but not more than might be expected on supportive therapy.

Group III: No effect. When the pelvic findings were essentially unchanged.

Group IV: Harmful result. When clinical evidence of exacerbation of infection followed therapy.

TABLE I. EVALUATION OF THE THERAPY

RESULT	TUBOOVARIAN INFECTIONS	CELLULITIC INFECTIONS		TOTAL
		MASSIVE	MODERATE	
Good	10	7	1	18
Doubtful	10	2	3	15
None	0	3	1	4
Harmful	4	0	1	5
Total	24	12	6	42

SUMMARY

1. Pelvic iontophoresis of a choline compound was given to 58 patients with subacute and chronic pelvic infection, all severe enough to warrant hospitalization; 37 were cases of tuboovarian infection and 21 were cases of cellulitis.

2. Subjective improvement was generally marked, and often out of proportion to objective evidence of decrease of the infection.

3. The results of therapy in tuboovarian infections, while often good, were not sufficiently remarkable to warrant routine use of this method of treatment. It seems clear that we cannot hope for resolution of old inflammatory tuboovarian masses, since fibrosis and multilocular cysts are a prominent part of the pathology. It may, however, be given a trial in persistent tuboovarian infections, when operative treatment is not indicated and other methods of treatment have been ineffective.

4. The best response to iontophoresis was seen in cases of massive cellulitic infection of recent origin which had failed to yield to ordinary treatment. Pelvic iontophoresis is recommended for this type of infection.

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A SURVEY OF FOUR HUNDRED AND TWENTY-FIVE CASES OF TOXEMIA OF PREGNANCY

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THE selection of a title adequately and accurately describing the work herein presented was difficult. We fully realize that the term "toxemia of pregnancy" denoting a "diagnostic trash can," is an ineffectual cloak for ignorance, and in the light of most recent investigation, is in all probability a misnomer. All of these opinions have been recognized and previously stated by others investigating the problem.

We do not feel that this survey will contribute anything new toward clarification of this maze, but present the series with the hope that it will in some measure add to the data already existent.

For want of a better term, and because it describes a syndrome familiar to the clinician and research worker alike, we too make use of the designation "toxemia of pregnancy," in the belief that this terminology will soon become obsolete in medical literature.

This series covers a ten-year period in the Department of Obstetrics at the New York Infirmary for Women and Children. During this time there were 7,293 deliveries, with a maternal mortality rate of 0.18 per cent. Of these deliveries, 425 occurred in women on whom a diagnosis of "toxemia of pregnancy" was made, in which group there was a mortality of 0.4 per cent. All of the cases presented occurred in the latter half of pregnancy, excluding therefore, pernicious vomiting of pregnancy which is included by others in discussing the subject of toxemia as a whole.

CLASSIFICATION

Our system of classification is one approved and accepted by the American Committee on Maternal Welfare, and we consider it to be simple and inclusive. Our cases are therefore grouped as follows: (A) pre-eclampsia, (B) eclampsia, (C) chronic nephritis, (D) essential hypertension (vascular), and (E) unclassified.

Although there are some people who do not feel that accurate classification can be based on the occurrence of hypertension, urinary abnormalities, and other findings in use as diagnostic aids, nevertheless, for the want of more satisfactory resources, we have depended to a certain degree on all of these factors. In addition to the clinical picture presented by the patient, we have carried out routine laboratory proce-

TABLE I. CRITERIA FOR CLASSIFICATION OF VARIOUS FORMS OF TOXEMIA

	PRE-ECLAMPSIA	ECLAMPSIA	CHRONIC NEPHRITIS	VASCULAR
Age	Usually young	Usually young	Usually older	May be any
Parity	Usually primiparas	Usually primiparas	Usually multiparas	May be either
History	Normal	Normal	Chronic	Normal or abnormal
Symptoms	*Same as eclampsia without convulsions	Headache Edema Irritability Dizziness Visual disturbances Nausea Vomiting Epigastric pain Suppression of urine Jaundice (rare) Convulsions	Headache Edema Polyuria Dizziness Visual disturbances	*Headache Edema Epistaxis
Onset	Late	Late	Early	Early
Blood pressure	Elevated Drops early	Elevated Drops early Diastolic high	Elevated Remains high Diastolic low	Elevated Remains high Diastolic high
Urine				
Albumin	1-2 plus	3-4 plus	1-4 plus	*1-4 plus
Specific gravity	Normal	High	Low and fixed	Varies
Microscopic	Usually negative	May have red blood cells, casts, pus	Casts	*Casts
Blood Chemistry				
Urea nitrogen	Normal	15-20	20-30	Little or no change
Uric acid	Normal (severe-elevated)	3.5-5 or more	3.5-5 or more	
Chlorides	Normal	Increased	Increased	
Proteins	Normal	Usually decreased	Decreased	
Urea clearance	Normal	Normal	Usually below 70%	Normal
Eye Grounds	Normal	Spasm of retinal vessels	Albuminuric retinitis	Arteriosclerosis

*May be variable or absent.

dures, and have taken into consideration the patient's past personal history, and have investigated the familial background. Wherever possible, especially during the past few years, we have included in our routine work-up an ophthalmologic consultation for opinion as to the findings in the fundus oculi.

MATERIAL

Our criteria for the division of cases into groups is outlined as shown in Table I.

Among our pre-eclampsias there are 116 cases which would in all probability be classified as "low reserve kidney" by Stander and his followers. In our hospital these patients are described as having pre-eclampsia of a mild degree.

In tabulating the groups, Table II will serve to illustrate the distribution of cases.

TABLE II

TYPE	PRIMIPARAS	MULTIPARAS	TOTAL
A. Pre-eclampsia	216	56	272
B. Eclampsia	13	3	16
C. Nephritis	41	69	110
D. Vascular	19	8	27

These findings coincide in the main with those published by other investigators with possibly one exception. We seem to have a higher incidence of chronic nephritis among our primiparous patients than is usually reported.

INCIDENCE

The age grouping in the series covers a wide range. It has usually been assumed that toxemia is an affliction of the young primipara, with the exception of the frequent occurrence of the nephritic type among older women, especially those who are multiparous. The ages of the patients presented in this survey range from 15 to 45. For simplicity the age incidence has been outlined graphically (Fig. 1).

MANAGEMENT AND THERAPY

The private cases totaled 70, leaving six times as many ward cases handled through the clinic and by the staff of the obstetrical department. The management of the private cases remained in the hands of the physician referring the case for hospitalization, but most of these were handled according to the departmental routine, and treatment, with very few exceptions, was essentially the same as that used in the service cases.

Most of the patients were treated according to the method now in use, which is described in detail later. There were, however, 62 patients admitted and delivered before any system of therapy could be instituted, and in these cases only the post-partum period was managed according to routine. In addition there were 38 cases occurring in the earlier years covered by this report that received a now out-dated mode of treatment. This method in the main comprised limitation of fluids,

hot packs, low protein diet, morphine in large doses, heavy catharsis, and in a few instances, venesection.

Due to the emphasis now being placed on registration early in pregnancy, and the awareness on the part of the laity of the importance of this, most of the cases delivered without benefit of ante-partum treatment likewise occurred in this early period.

Our present routine in the clinic is begun as early as the symptoms appear, and every physician working in the clinic is on the lookout for danger signs.

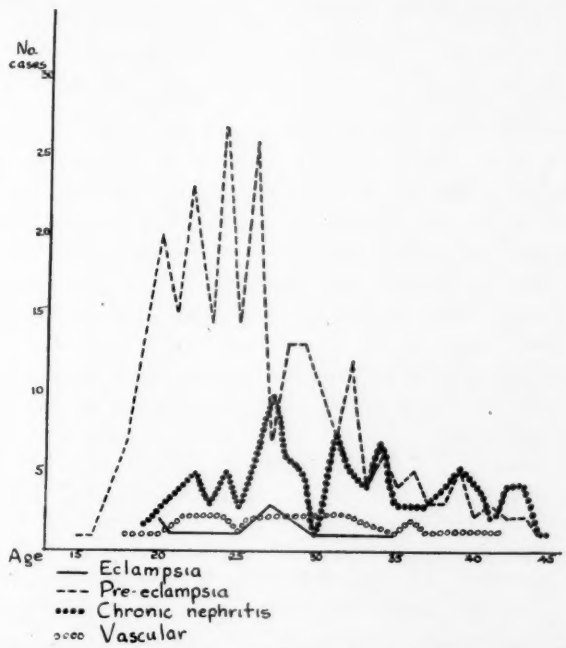

Fig. 1.—Graph showing incidence of various types of toxemia according to age.

Upon admission every obstetric patient receives a complete physical examination plus detailed investigation concerning the past personal and familial history, with special reference to hypertension and cardiovascular renal disease. Those patients in whom there is a history of previous cardiovascular renal disease, whose family shows a prominent history of the same, or in whom there is a history of previous pregnancy complicated by hypertension, renal disease, or toxemia as such, are designated for further study and close observation.

In investigating the personal histories of the patients included in this series, the following significant factors in their past histories were elicited: cardiac disease in 17, numerous infections in 36, spontaneous abortions in 46, pyelitis in 5, previous stillbirths in 7; convulsions, thyroid dysfunction, sterility, 2 each; syphilis, tuberculosis, diabetes, 1 each.

In any patient showing clinical signs of potential or actual toxemia, special attention and immediate action is our rule. Every clinic visit during the prenatal period includes a urinalysis, determination of

blood pressure, check of the gain in weight, and examination on the table. In the course of this examination the height of the fundus is measured, the heart examined, and the presence or absence of edema noted. In addition, each patient is questioned carefully to elicit any complaint. Specific questions are asked concerning gastrointestinal upsets, headache, visual disturbances, dizziness, undue irritability, and swelling of any part of the body. When a patient presents any finding which indicates that she presents a potential or actual toxemia, she is seen by the attending physician or resident and placed on the routine proper for her phase of the condition.

To clarify the terms "potential" and "actual" toxemia as recognized in our clinic, we refer to the history, both personal and familial, and consider in addition the general physical constitution as to endocrine type of the patient. In patients whose physical type or history would seem to predispose to some form of toxemia a designation of potential toxemia is made. This group is given explicit instruction as to diet, rest, sodium chloride intake, and fluid intake and output. In addition these patients are impressed with the importance of keeping clinic appointments and are followed by Social Service to insure regular visits. Wherever indicated basal metabolic rates are taken and thyroid administered if necessary.

Patients considered actual toxemias are those presenting recognized symptoms or signs in any degree. Symptoms presented by the cases in this series included the following: edema, nervous irritability, visual disturbances, headache, dizziness, epistaxis, gastric disturbances, jaundice, and convulsions. There were a few patients, three of whom proved to be true eclamptics, who denied complaint and who presented no premonitory signs whatever until the actual seizure. In all patients excessive weight gain, elevation of blood pressure, and albuminuria were considered of diagnostic import.

Edema was by far the most common and often the earliest manifestation. It is interesting to note that 196 patients complained of only a single symptom as outined: edema, 168; headache, 13; dizziness, 4; gastric disturbance, 4; visual disturbance, 4; epistaxis, 1.

Of those patients with a completely symptom-free picture, 36 were in the pre-eclamptic group, 12 were chronic nephritics, 3 were eclamptics, and 5 were in the vascular group. Twelve of these patients have been followed since delivery and to date 5 show definite evidence of permanent cardiovascular renal damage.

Potential cases are seen frequently in the clinic and watched carefully for signs or symptoms which might appear and place them in the group of actual toxemias.

In the patients with early mild symptoms, the following constitutes our preliminary regime:

1. Addition of protein and carbohydrate to the diet.
2. Advice as to adequate rest.
3. Administration of magnesium sulfate in four dram doses to be taken once daily.
4. Limitation of the intake of sodium chloride to only the amount used in cooking.

These patients are instructed to report to the clinic after two weeks of this routine at home with warning to return earlier if necessary. If such a case is seen in the clinic after her two-week interval and shows no abatement of symptoms, or shows an aggravation of the condition, she is placed on a more rigid regime to be carried out at home if possible. Lack of space, a busy service, and in many cases the patient's home conditions prohibit routine hospital admission, although this would undoubtedly be the desirable procedure. The course followed under these circumstances involves cooperation with the local Visiting Nurse Service. The patient is sent home for absolute bed rest, and the visiting nurse requested to make frequent home visits. At these visits the patient is questioned as to complaints, blood pressure reading is taken, and urine examined for albumin. The nurse in turn reports to our clinic. In addition the following instructions are given:

1. Dietary restrictions and additions are reviewed.
2. Sodium chloride is eliminated entirely and potassium chloride substituted for palatability.
3. Phenobarbital is prescribed in 0.5 gr. doses three times daily.
4. Magnesium sulfate is continued in the same amount.
5. Calcium lactate is given in 10 gr. doses three times daily.
6. Absolute bed rest is stressed as imperative.

Vitamin B and iron are given routinely to all prenatal cases.

Patients so managed are told to report in one week to the clinic and in many cases improvement is noted. However, if there is no improvement, or if the case shows progression, hospital admission is then considered imperative.

The routine on the ward is essentially the same as that outlined for clinic management. In addition, intravenous glucose or glucose and magnesium sulfate as formulated by McNeil is given. In the hospital adequate supervision is the most valuable added factor.

In the past few years patients who had persistent appreciable amounts of pus in the urine, or who showed other signs or symptoms of pyelitis, were cystoscoped and wherever possible retention catheters were inserted to facilitate drainage. Nine such procedures were done in this group.

Many of the patients in this series remained from one to two weeks in the hospital and showed sufficient improvement to warrant discharge before delivery. These were followed satisfactorily in the clinic until term. However, cases near or at term on admission for treatment were usually considered as fit subjects for induction as soon as their condition made this possible. Medical induction, or medical induction followed by artificial rupture of the membranes, with or without the introduction of a Voorhees' bag, was the method of choice. A few patients were subjected to cesarean section purely because of the fulminating state of the toxemia.

During labor all toxemias are watched with particular care, and blood pressure determinations are taken at intervals of one to two hours. Adequate sedation is given, consisting usually of morphine in one-sixth grain doses with atropine in doses of 1/150 grain. This is supplemented toward the end of the first stage by rectal instillation of

plain ether in oil in the milder cases. Gas-oxygen or drop ether, the former generally considered more desirable, is administered with pains during the stage of expulsion. Immediately following delivery of the placenta, the patient is again given morphine if necessary.

When convulsions occurred prior to delivery, all concern was naturally for the mother. In the cases occurring earlier in the series presented, ether was administered during the seizure and morphine was immediately given. These procedures were followed as soon as practical by intravenous administration of glucose and magnesium sulfate. The tendency at the present time is to give oxygen rather than ether and to omit morphine if possible because of the additional cerebral edema produced by the drug. Rest in a quiet location with constant attendance is still the rule.

In this series, there was a total of 16 convulsive cases distributed as follows: 3 ante partum, 6 intrapartum, and 7 post partum. In one case in which convulsions occurred five days post partum in a recurrent toxemia, oxygen through a nasal catheter produced such dramatic results and so much comfort was experienced by the patient that its use deserves special mention.

Regular blood pressure readings are taken on all post-partum cases and recorded twice daily. These patients are watched carefully for persistence, recurrence, or aggravation of signs and symptoms of toxemia. Blood chemistries are repeated as often as necessary and the routine continued as long as there are indications of active disease. All patients with toxemias are instructed on discharge to report both to the post-partum and medical clinics.

The use of phenobarbital is discontinued as soon as the patient shows definite lowering of blood pressure. In the vascular and nephritic types where there is frequently no fall in blood pressure, it is discontinued after three or four days. This has been done because of the depression often found with long-continued administration of the barbiturates.

The number of cases induced was 42 (9 per cent). Most of the patients admitted were able to return to their homes after treatment to be readmitted in spontaneous labor. Others went into labor while under treatment in the hospital.

Reports on the method of delivery in many hospitals show a high incidence of operative delivery. Of our 425 cases, 321 delivered spontaneously, leaving 24 per cent assisted deliveries. The methods of operative delivery included the following: Cesarean section, 21; low and midforceps, 66; breech extractions, 8; version and extraction, 8. Seventeen of the cesarean sections were performed for reasons other than the toxemia itself, including cephalopelvic disproportion, placenta previa, and premature separation of the placenta. Statistics in other hospitals show a larger percentage of operative delivery to be found among patients handled by private physicians. This does not seem so apparent in our group, with 3 per cent incidence among private deliveries and 2.3 per cent among the service cases.

COMPLICATIONS

Among the complications encountered were the following: pyelitis, 9 cases; premature separation of the placenta, 5; placenta previa, 2; post-partum shock and post-partum psychosis, 1 each.

Work has been done recently in an attempt to correlate the existence or history of pyelitis with toxemias of pregnancy. While a great many of our patients had small amounts of pus in casual urine specimens, there were only 9 cases presenting a true pyelitis during the course of the toxemia. Five patients had a history previous to the toxic state. In the follow-up of 109 toxic cases, 3 patients had pyelitis during a subsequent pregnancy. Two of these patients had recurrent toxemia of mild degree, complicated by the pyelitis, and one was a patient with recurrent toxemia, terminating in death from pyelonephritis.

MORTALITY

With the recent increased interest in maternal and infant mortality, it is pertinent to discuss our results and to correlate wherever possible the influence of induction and operative delivery with these results. There were 2 immediate maternal deaths in the series, giving a mortality rate of 0.04 per cent. One of these patients was delivered by cesarean section and the other delivered spontaneously. These deaths are presented in detail.

CASE 1.—M. B., white primipara, unmarried, 38 years of age, was seen for the first time as an emergency on the day of admission. At this time she was seven months pregnant. She had been treated at home by a physician for "yellow jaundice" of three days' duration, at which time she was told that her blood pressure was high and that there was albumin in the urine. Her past history was significant in that she had suffered recurrent respiratory infections, and two years previously had had a cerebral accident with hemiplegia on the right side.

On admission the blood pressure was 205/110. The skin was dry and yellow, and there was marked pitting edema of both legs. The laboratory findings revealed blood urea nitrogen to be 53 mg. The urine showed four-plus albumin, with many hyalin and granular casts.

The patient was placed on the old routine of liquid diet, hot packs, and colonic irrigations. Eight hours after admission she complained of pains in the neck and severe occipital and frontal headache. The following day the patient's appearance was poor, and there was some vaginal bleeding accompanied by uterine contractions and pain. A diagnosis of premature separation of the placenta was made and classical cesarean section was performed under ethylene anesthesia. The infant was stillborn and weighed 3 pounds and 11 ounces. During the operation, the blood pressure fell from 226/140 to 150/110.

The immediate postoperative condition was fair. Twenty-four hours after operation the patient complained of diminution of vision and thirty-six hours after operation she became stuporous. The blood pressure at this time was 186/124. Forty-eight hours after operation the patient died.

Autopsy findings consisted of hemorrhagic hepatitis of the eclamptic type and extensive tubular degeneration of the kidneys. Permission for examination of the head was not obtained.

CASE 2.—A. P., white, married, primipara, 24 years of age, was first seen in the third month of pregnancy, symptomless except for occasional nocturia. Past history revealed one spontaneous abortion ten months previous to clinic admission. At the time of admission her weight was 168 pounds, height 5 feet 1 inch. Her blood pressure was 120/70.

In the fourth month of pregnancy, she complained of ankle edema and dyspnea, although there was no change in the blood pressure. Urinalysis was negative and

cardiac consultation revealed no abnormality of the heart. At this time she had gained a great deal of weight and magnesium sulfate was given by mouth. There was apparent improvement until the ninth month.

Early in the ninth month the patient was admitted to the hospital with ruptured membranes and no pains. At this time the blood pressure was 140/92 with slight pitting edema of the ankles. The urine showed four-plus albumin and no pus. Labor was initiated by medical induction, and after thirty-three hours she was finally delivered by midforceps operation of a living baby, weighing 8 pounds. Her postpartum period was uneventful and blood pressure on discharge was 126/80.

In spite of contraceptive advice, this patient returned nine months later in the fourth month of her third pregnancy at which time her blood pressure was 114/62. From the middle of this pregnancy, there was an excessive gain in weight. During the eighth month urinalysis revealed three-plus albumin, and there was evidence of hydramnios with edema of the abdominal wall. The blood pressure had risen to 134/90, and she complained of dizziness and blurring of vision. She was admitted to the hospital.

In addition to the ward routine the patient had cystoscopic examination. The membranes ruptured spontaneously, and after a labor lasting sixteen hours she was again delivered by midforceps under gas oxygen anesthesia of a 13-pound stillborn infant. During labor the blood pressure varied between 190/110 and 120/80. Examination of the fundus oculi showed only spasm of the retinal vessels. The condition of the patient following delivery was poor, and in spite of supportive treatment death occurred ten hours later. Blood culture before death was positive for *B. coli*.

Autopsy findings revealed advanced bilateral acute pyelonephritis with hemorrhagic cystitis in addition to septicemia, early bronchopneumonia, and congestion of liver and spleen as well as generalized anasarca.

Two patients in this series died later of causes dependent upon and associated with previous toxemia. These are presented in detail.

CASE 3.—G. W., white, married, primipara, 34 years of age, was first seen in the clinic in the eighth month of pregnancy, weighing 181 pounds. On clinic admission physical examination was negative. Laboratory findings were normal and blood pressure was 118/72. Her condition was considered normal until the time of hospital admission.

On admission in the first stage of labor the blood pressure was 154/110. Urinalysis showed some pus and a trace of albumin. The blood chemistry showed urea nitrogen of 14 mg. and uric acid of 2.4 mg. At this time a soft systolic murmur was heard at the apex. Labor was extremely irregular, with intervals of complete cessation of pains. After sixty-two hours of ineffectual labor, manual dilatation of the cervix and delivery by midforceps was carried out, and a living baby obtained. The blood pressure after delivery was 134/95 and the urine showed a moderate amount of albumin. Dilution and concentration tests showed poor concentration. The puerperium was clinically normal.

Three years later this patient was admitted to the surgical department with the diagnosis of acute appendicitis. The blood pressure at this time was 116/66, urine showed a trace of albumin and a few casts. The urea nitrogen was 16.8 mg. and uric acid 2.5 mg. Her interval history was negative.

After appendectomy, the patient became semicomatose, and thirty-six hours after operation a slight asymmetry of the face was apparent, with inequality of the pupils, blurred speech, and flaccidity of the left upper extremity. The patient died forty-eight hours after operation.

Autopsy revealed thrombosis of the right middle cerebral artery, with softening of the right cerebral hemisphere, general cerebral arteriosclerosis, and generalized arteriosclerosis. There was also old rheumatic mitral valvulitis and cardiac hypertrophy (Fig. 2).

CASE 4.—V. C., white, primipara, married, 21 years of age, was first seen in the clinic in the fourth month of her pregnancy. Her past history was negative, but

there had been occasional swelling of the feet during her pregnancy. On her first visit the blood pressure was 116/70. She was referred to the dental clinic for treatment of marked dental caries.

Two weeks later urinalysis showed two-plus albumin; the blood pressure was 120/78; she had gained 6 pounds. At this time she complained of moderate ankle edema and nausea. She was admitted to the hospital whereupon her urine showed four-plus albumin, many pus cells and hyalin casts. Her hemoglobin was 55 per cent Sahli; blood urea nitrogen, 37.9 mg.; uric acid, 4.8 mg. In addition to the current routine, the patient was cystoscoped and a retention catheter inserted on the left side; the right ureteral orifice could not be identified. Urine culture showed the presence of *B. coli*. The eye grounds were found to be negative. Transfusion a few days later was followed by severe reaction. Sulfanilamide therapy was instituted.

Twelve days after admission labor intervened with the delivery of a five months' stillborn fetus. Following delivery, her temperature rose to 102° F. for two days and the blood pressure was 116/100. Ten days after delivery blood urea nitrogen was 88 mg. and uric acid 6.7 mg. The patient refused to remain in the hospital any longer and signed out under protest.

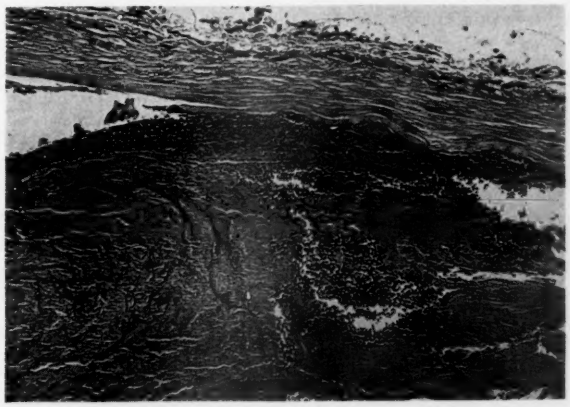

Fig. 2.—Case 3. Photomicrograph showing thrombosis in right middle cerebral artery.

Five months later she was admitted to the medical service with edema of the lower extremities. At this time she showed a clinical picture typical of chronic nephritis. After treatment she improved and was discharged from the hospital and never seen again. Reports have come to us recently that the patient died during an episode similar to that above approximately two years after delivery.

Fetal mortality is always reported as being high in the toxemias of pregnancy, especially in the eclamptic group. The London Committee reports a fetal mortality of 34.8 per cent in eclampsia, and Stander reports mortality figures of 30 per cent in the same group. Tillman and Watson found the highest figures occurring among the nephritic types where the mortality was 69 per cent. Cruikshank, Hewitt, and Couper found the neonatal mortality rate in eclampsia to be 17 per cent for mature infants and 54 per cent for premature infants. In our series there were 39 stillbirths for the entire group, an incidence of 9.6 per cent. Eighteen of these cases were macerated, and 5 were due to causes other than the toxemia. There were 15 neonatal deaths, an incidence of 3.5 per cent.

Among the 42 induced cases there were 2 stillbirths and 2 neonatal deaths. Of those patients delivered by operative methods, there were 14 stillbirths and 7 neonatal deaths. This leaves us with the remainder, numbering 23 stillbirths and 9 neonatal deaths, which occurred in spontaneously delivered patients in whom labor was initiated without interference. The stillbirth incidence in spontaneously delivered patients was 0.4 per cent and the incidence of neonatal mortality was 0.19

per cent. The incidence of stillbirths in patients delivered operatively was 0.29 per cent and the neonatal rate was 0.19 per cent. These are corrected readings and do not include macerated fetuses.

Among 21 patients induced before 38 weeks, 21 living babies were obtained. Of these babies, 2 died in the neonatal period, 1 from prematurity and 1 from congenital deformities constituting a monstrosity. In addition, there was 1 macerated stillbirth in a set of twins. Seventeen of the stillbirths occurred in pre-eclamptic mothers, 1 in a true eclamptic, and there were 2 each in chronic nephritic and vascular types. Seven of the neonatal deaths occurred in babies delivered of pre-eclamptic patients, 2 from eclamptic patients, and 6 from nephritic and vascular forms of toxemia.

Among the causes of stillbirth other than toxemia were the following: prematurity and tentorial tears, 2 each; impacted shoulders, congenital edema, placenta previa, premature separation of the placenta, 1 each. Among the causes of neonatal death other than toxemia were: prematurity, 8; monstrosity, 3; congenital cardiac anomalies, 2; and neurocytoma, 1.

One hundred and six examinations of the fundus oculi were done. Of these, 58 showed fundi indicating changes in the vascular system. Our attempts to use our findings as diagnostic aids and prognostic signposts were somewhat disappointing as borne out by the information obtained in following our cases. Seventeen patients in whom positive eye findings were noted during the toxemia have remained so, while one who was positive at the time of her toxic pregnancy has since become negative. Of 15 patients with negative findings during the original onslaught of the disease, 13 on subsequent examination showed vascular changes.

FOLLOW-UP

In following our patients, we found recurrence to be much more frequent than has been generally reported. Many women showed evidence of permanent damage to the cardiovascular renal network, although a diagnosis of mild toxemia only had been made at the time of the admission to the obstetrical department. These follow-ups have covered a period of from one to seven years and total 109 cases. In the entire series 33 patients were actually recurrent toxemias, having originally come to us with the history of previous renal disease or true toxemia in a previous pregnancy. In addition, 71 patients later showed demonstrable evidence of damage as a result of their one toxic pregnancy. This statement is made on the basis of results obtained from blood chemistry examination, urinalysis, eye ground changes, and physical examination.

Of those patients returning with subsequent pregnancy, there were 28 in whom recurrence of the toxemia was evident, and only 8 with no demonstrable signs of recurrence. All these patients received careful supervision and were given all known prophylactic measures to prevent a return of the condition.

SUMMARY

We have presented a series of cases, numbering 425, termed loosely and possibly incorrectly "toxemia of pregnancy." No attempt is made to discuss the etiology. The classification used is standard.

Our methods of management, past and present, are outlined, admittedly conservative, from the earliest prenatal period to the final stage of delivery and puerperium.

Complications occurring in the mother and infant are presented and discussed; mortality statistics for both are given. From our follow-up,

we have felt that recurrence is more frequent than formerly thought. It is to be stressed that damage to the cardiovascular renal system is often of far-reaching consequence, even in supposedly mild cases of toxemia of pregnancy.

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TRANSVERSE PRESENTATIONS*

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THE development of obstetrics as an art has always been intimately blended with the condition of a people and the progress of their civilization. A certain perfection was attained even by primitive peoples, but quite strangely no real progress was made from the time of Hippocrates in Greece and the Ayur Veda in India until Paré and Vesalius laid the foundation of modern scientific obstetrics in the middle of the sixteenth century. Paré rediscovered podalic version in this period when empiricism gave way to scientific research with the study of anatomy and physiology and the acceptance of obstetrics as one of the branches of medical science. The use of the destructive operation as the only solution to a difficult labor was soon replaced by attempts to save the life of the child by version or forceps, and as a result the transverse and oblique presentation of the child became less formidable. More accurate knowledge of the pelvis, the uterus and the forces concerned in the expulsion of the fetus allowed a more scientific approach to the proper handling of abnormal presentations.

Many causative factors enter into the determination of the manner in which the fetus lies in utero. The occurrence of a transverse presentation with the long axis of the child crossing the long axis of the mother, usually obliquely, but occasionally at right angles, is fortunately not too common. This type of abnormal presentation occurs about once in every 200 to 250 cases. Factors preventing engagement of the fetal head in the pelvis and conditions allowing unusual mobility on the part of the fetus are perhaps responsible for the majority of instances of this error of polarity. Disproportion between the pelvic inlet and the fetal head must be immediately looked for, whether due to contraction of the bony pelvis or increased cephalic dimensions. This is true particularly in primiparas, but must also not be overlooked in the patient who has previously borne children normally. Obstructive pelvic tumors and low implanted placentas are occasionally encountered as the cause of unusual presentations. Uterine malforma-

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tions and fetal anomalies may play a part in the failure of a fetus to present correctly and must constantly be borne in mind when encountering the fetus which lies abnormally in the uterus. An excessive amount of mobility of the fetus making for variations from the normal cephalic presentation is often associated with multiple pregnancies, multiparity with its relaxed uterus and abdominal wall, premature labor or polyhydramnios. Not infrequently several causes may be associated with the failure of a fetus to present correctly. A word must be said about pure accident as a cause of abnormal presentations. The rupture of the amniotic sac at a time when the fetus lies in an unusual position will sometimes cause a shoulder presentation associated not infrequently with the prolapse of an extremity or umbilical cord.

The so-called oblique presentation often corrects itself early in labor and spontaneously becomes converted into a vertex or a breech presentation. The true transverse presentation may rarely terminate spontaneously if the child is very small or macerated. The child is almost always stillborn. This delivery by spontaneous evolution is too rare to be relied upon except in the instances cited above.

De Lee states that version, not expectancy, is the treatment of transverse presentations. Posture, external version before the onset of pains or early in labor, the use of a properly applied binder, or the application of a Willett clamp to the fetal scalp following external version are all useful procedures if intelligently employed in indicated situations. Under proper circumstances internal podalic version and breech extraction is the procedure of choice. The dilatation of the cervix and the amount of amniotic fluid are among the important factors to be considered.

The neglected transverse presentation presents an entirely different problem from the case which is correctly handled throughout. The danger of serious fetal and maternal complications in the former, not

TABLE I. DISTRIBUTION OF CASES ACCORDING TO PARITY, AGE OF MOTHER, DURATION OF PREGNANCY, AND TYPE OF PELVIS

FINDINGS	NUMBER			PERCENTAGE DISTRIBUTION		
	TOTAL	WHITE	COLORED	TOTAL	WHITE	COLORED
Parity:						
Gravida i	18	10	8	11.9	12.2	11.6
Gravida ii	26	14	12	17.2	17.1	17.4
Gravida iii to v	55	32	23	36.4	39.2	33.3
Gravida vi or more	52	26	26	34.5	31.5	37.7
Age Distribution:						
Below 20 years	11	5	6	7.3	6.1	8.7
20-31 years	78	44	34	51.7	53.7	49.3
32-35 years	33	13	20	21.9	15.9	29.0
36 years or more	29	20	9	19.1	24.3	13.0
Duration of Pregnancy:						
Less than 28 weeks	5	3	2	3.3	3.7	2.9
28-32 weeks	10	6	4	6.6	7.3	5.8
33-36 weeks	25	13	12	16.6	15.9	17.4
37-39 weeks	16	10	6	10.6	12.2	8.7
40 weeks	95	50	45	62.9	60.9	65.2
Pelvis:						
Normal	144	80	64	95.4	97.6	92.8
Contracted	7	2	5	4.6	2.4	7.2

infrequently associated with a ruptured uterus or a destructive operation on the child, is in marked contrast to the satisfactory results for all concerned if good obstetric art is employed.

Realizing the dangers associated with this abnormality in the polarity of the fetus in utero, it was decided to review the transverse presentations occurring at the University Hospital in Baltimore from June 1, 1920, to Dec. 31, 1939 (Table I).

STATISTICS

During this period of time there were admitted to the hospital 151 cases of shoulder presentation. Eighty-two of these occurred among white patients, and 69 among colored, 54.3 and 45.7 per cent, respectively. One hundred and thirty-three of the 151 patients were multiparas, and 70 per cent of these were gravida iii or more. In fact, more than a third of the patients were gravida vi or more. Thus, multiparity as a well-known factor is borne out in our series.

In so far as age is concerned, the age group of 20 to 31 years predominated and contained over half of the cases. Only 11 of the patients were below 20 years of age and almost one-fifth of the series were 36 years or older. The youngest age group was about evenly divided between white and colored but the oldest group of 36 years or more was almost twice as large in the white group as in the colored.

Multiple pregnancy occurred 10 times or an incidence of 1 in 15 in contrast to the frequency of about 1 in 80 normally encountered for twins. The duration of pregnancy at the time of delivery shows that 37.1 per cent of the fetuses were not at term. This presence of an undersized fetus in more than one-third of the cases combined with a preponderance of multiparas bears evidence of at least some of the factors concerned in the cause of shoulder presentations.

Contraction of the pelvis was encountered in an extremely small number of instances, only 7 patients showing considerable pelvic contraction, a percentage of only 4.6. Five of these 7 were in colored patients. Other series reported show a larger figure than this, and the importance of pelvic abnormality must not be minimized.

The length of time which the membranes have been ruptured has always been felt to be a most important consideration in determining the method of handling a particular case. This event, allowing the escape of amniotic fluid with its resultant closer application of the uterus to the fetus and the greater likelihood of bacterial invasion of the birth canal, is of prime importance. In our series 60.3 per cent of the patients had either an intact bag of waters or membranes ruptured less than six hours. Of the remainder, 17.2 per cent had membranes which had been ruptured twenty-five hours or longer upon admission to the hospital. Results for both mother and child are far too frequently affected seriously by a prolonged attitude of hopeful expectancy prior to hospitalization which eventually leads to unpleasant consequences, entirely avoidable in many instances if more intelligent methods had been employed. Neglected cases with their resultant retraction rings and ruptured uteri are admitted to every clinic frequently enough to impress upon everyone the consequences of a failure to make an early diagnosis and to properly treat this complication when it is encountered.

Many of the patients in this series were admitted to the hospital after being improperly handled. A prolonged period of labor, membranes ruptured for many hours, a variable amount of cervical dilatation, and a prolapsed extremity or cord characterized a number of admissions. Thus, the type of treatment of necessity varied tremendously, and many procedures were necessary which would have never occurred had an opportunity been available for the intelligent handling of the case from the start. External version was possible in 17 instances, internal podalic version and breech extraction was resorted to 87 times, or 57.6 per cent of the cases. Twenty-three cesarean sections were done, and 12 destructive operations were necessary. In 6 instances, spontaneous delivery occurred without interference on the part of the operator. These were in the presence of small and usually macerated

fetuses. There were several instances in which the Willett clamp was applied to the fetal scalp with most satisfactory results. Before the value of hysterostomatomy was appreciated as it is today, severe cervical laceration with its resulting hemorrhage was far too frequently encountered, but in recent years prophylactic incision of the cervix in properly selected cases is a well worth-while procedure. In our series severe cervical tears occurred 11 times, and actual rupture of the uterus 4 times. These latter will be considered in more detail later on.

One of the most important considerations in any discussion of pathologic complications of pregnancy is the maternal and fetal morbidity and mortality. In this series 42 of the patients showed an elevation of temperature of 100.4° F. on two or more occasions following delivery, excluding the first twenty-four hours post partum, giving us an uncorrected morbidity rate of 27.8 per cent. Four of the mothers died, a maternal mortality of 2.6 per cent. There were 114 full-term infants, 35 of which were stillborn, a percentage of 30.7. Of the 37 premature fetuses, 19, or 51.4 per cent, were stillborn. Of the total number of liveborn, 13, or 13.4 per cent, died within ten days of birth. Excluding the deaths among premature infants from this group, the infant mortality rate for the first ten days was 6.1 per cent.

TABLE II. DISTRIBUTION OF CASES ACCORDING TO DURATION OF LABOR AND EFFECT ON CHILD

DURATION OF LABOR AT TIME OF DELIVERY	NUMBER			PERCENTAGE DISTRIBUTION			RESULT OF DELIVERY			
							NUMBER		RATE PER 100 CASES	
	TOTAL	WHITE	COLORED	TOTAL	WHITE	COLORED	STILLBORN	LIVEBORN	STILLBORN	LIVEBORN
Not in labor or less than 6 hours	41	26	15	27.2	31.7	21.7	7	34	17.1	82.9
6-11 hours	40	25	15	26.5	30.5	21.7	16	24	40.0	60.0
12-23 hours	33	16	17	21.9	19.5	24.6	11	22	33.3	66.7
24 hours or more	37	15	22	24.4	18.3	32.0	20	17	54.0	46.0
All cases	151	82	69	100.0	100.0	100.0	54	97	35.7	64.3

A most interesting observation is the relationship between the duration of labor at the time of delivery and the infant mortality. Of the entire series, 41 patients, or 27.2 per cent, were not in labor or were in labor less than six hours; 26.5 per cent were in labor six to twelve hours; 21.9 per cent in labor thirteen to twenty-four hours; and 24.4 per cent for twenty-five hours or longer. The prolonged labors were far more common among the colored patients showing definite evidence of less proper care. The effects of this prolongation of labor on the number of stillbirths is borne out by a percentage of 17.1 stillborn fetuses among the group of patients not in labor or in labor less than six hours, as compared to a gradually higher figure as the duration of labor increased. In the group of patients in labor twenty-five hours or more, the percentage of stillborn children was 54.

The relationship between the type of delivery and the condition of the child at birth is also important. In 17 patients the shoulder presentation was corrected by external version, and in this group of patients, only 5.9 per cent of the babies were stillborn. On the other hand, in 87 cases in which internal version and breech extraction was the method of delivery, 32.2 per cent of the babies were stillborn. This clearly demonstrates the danger of this procedure, particularly since 2 of the 4 maternal deaths and 3 of the 4 ruptured uteri, in the entire series, occurred in patients on whom version and extraction was done.

A word or so concerning the instances in which a rupture of the uterus or a maternal death occurred should be of interest.

CASE 1 (10206).—A white, para 3-0-1-2, aged 28 years, had a negative serologic test for syphilis; pelvis was normal. A full-term fetus lay in the transverse position and after forty-seven hours of labor the cervix was 8 cm. dilated, and the membranes were unruptured. An internal podalic version and breech extraction was done with considerable difficulty; the child delivered up to the head when more difficulty was encountered. The head was finally delivered but the fetus was stillborn. Examination of the patient revealed a severe tear in the cervix extending into the lower uterine segment. A laparotomy was performed, revealing a tear into the right broad ligament, and a hysterectomy was immediately done. The patient stood the procedure well, had an uneventful convalescence, and was discharged from the hospital in fifteen days in good condition.

Comment.—The combination of poor prenatal observation, neglect during a long labor, and poor judgment at the time of delivery was indeed sufficient to account for the results obtained in this case. The incompletely dilated cervix was ignored and this probably accounted for much of the difficulty. Hysterostomatomy might have avoided the severe laceration and stillborn child. Only good fortune can be credited with a live mother following this type of unintelligent treatment.

CASE 2 (11130).—A colored, para 9-0-0-8, aged 38 years, serologic test for syphilis negative, pelvis normal, was admitted to the hospital from the outpatient department after having been in labor for thirty hours. The membranes ruptured spontaneously one hour after the onset of labor. The pregnancy was at term and the presentation was transverse. On admission, the cervix was found to be fully dilated and the elbow prolapsed into the vagina. A diagnosis of a Bandl's ring was made which seemed to relax under deep anesthesia. An internal podalic version and breech extraction was done without difficulty and a full-term live child was delivered. The third stage was normal, but on exploring the uterus routinely, a laceration was discovered in the lower segment which extended into the broad ligament. A hysterectomy was immediately done. The patient stood the operation well, but the puerperium was quite stormy. After seventeen days, both mother and baby left the hospital in good condition.

Comment.—Here again it is obvious that hopeful expectancy was depended upon with deleterious results. The version and extraction following a prolonged labor with ruptured membranes resulted in a rupture of the uterus. Correction of the transverse presentation early in labor by external version combined with the use of a binder or a scalp forceps might very well have resulted more favorably and placed the patient in less jeopardy.

CASE 3 (24962).—A colored, para 6-0-0-6, aged 33 years, with a serologic test for syphilis negative and pelvis normal, was admitted in labor. Labor began at 2:00 A.M., membranes ruptured at 6:30 A.M., and at 8:30 A.M. a hand prolapsed. She bled about 200 c.c. at this time and showed mild shock. On admission, it was found that there was a shoulder presentation, with the cervix fully dilated. There was some dullness in the left flank on percussion at this time. The fetal heart was absent and the general condition of the patient was very poor. Intravenous glucose and blood were given in an attempt to improve the patient's condition for operation, since a ruptured uterus or a premature separation was fairly obvious. The patient suddenly became pulseless and respirations labored. Following transfusion, she rallied considerably, and a full-term stillborn child was delivered by internal podalic version and breech extraction. Exploration of the uterine cavity revealed a rupture on the left side. Hysterectomy was immediately performed, but the condition of the patient was so poor that little hope existed for her recovery, and she died shortly after the operation was completed.

Comment.—Earlier recognition of a rupture of the uterus and elimination of the delivery by the vaginal route might have resulted differently in this case. This, of course, is not by any means a certainty, since the general condition of the patient was critical on admission to the hospital. Again, an early diagnosis of a transverse presentation followed by its correction if possible might have avoided much of the difficulty.

CASE 4 (83041).—A white, para 1-0-0-1, aged 30 years, had a negative serologic test for syphilis and a normal pelvis. The patient was brought to the hospital by her private physician. Her membranes had been ruptured for ten days according to him, and labor had begun twelve hours previous to admission. The labor pains which had been good since their onset slowed down somewhat, and a full ampoule of pituitrin was given. Within a few minutes, a hand protruded from the birth canal, and on admission to the hospital shortly thereafter, the uterus was tetanically contracted, the child presented transversely, and the heartbeat was absent. Deep anesthesia was administered and a Bandl's ring was palpated through a fully dilated cervix. Following a destructive operation, a full-term child was extracted with difficulty. Exploration of the uterus revealed a rupture in the lower segment. Hysterectomy was immediately performed. In spite of repeated transfusions and oxygen the patient did badly and died three days following operation.

Comment.—This is another example of the incorrect way to treat a transverse presentation. Failure to diagnose the presentation, the administration of pituitrin injudiciously, and the unwise attempt to deliver from below in the presence of a tetanically contracted or already ruptured uterus, all played a part in the tragic results in this case.

CASE 5 (32563).—A colored, para 6-0-0-6, aged 33 years, with a serologic test for syphilis negative and pelvis normal, was admitted to the hospital from the outpatient department with a transverse presentation and a prolapsed hand. On admission, the membranes had been ruptured twenty-seven hours, and the cervix was about two-thirds dilated, pains having begun shortly after the membranes ruptured. The patient was anesthetized, the cervical dilatation was completed manually and a premature live child was delivered with difficulty by internal podalic version and breech extraction. Twenty-five minutes later the patient began to bleed profusely, losing over 1,000 c.c. of blood. Oxytocics and intravenous fluids were given, and even though the bleeding ceased, severe shock developed quickly, and two hours from onset of the hemorrhage, the patient died. Autopsy was refused but post-mortem examination of the birth canal failed to reveal any laceration in the cervix or uterus.

Comment.—The various errors in the treatment of this patient, such as the expectant attitude in dealing with a transverse presentation, the prolonged labor and rupture of the membranes, the accouchement forcé followed by a version and breech extraction, all contributed to the death of this patient. One is inclined to suspect that a failure to diagnose a tear in the lower uterine segment occurred at the post-mortem examination.

CASE 6 (35978).—A colored, para 1-0-0-1, aged 19 years, serologic test for syphilis negative and pelvis normal, was sent to the hospital by her family physician with a history of her membranes having ruptured three days, and labor having commenced about thirty hours prior to admission. On vaginal examination, seven hours after the onset of labor pains, he discovered a shoulder presentation which he attempted to correct by pressure from below. Several hours later another vaginal examination revealed an arm prolapsed into the vagina, and the patient was hospitalized. The patient was at term, a transverse presentation was obvious on abdominal examination, the fetal heart was heard, and the uterus was tetanically contracted with evidence of a thinned-out lower uterine segment. The administration of oxytocics was denied. A classical cesarean section was done following which the patient ran a very stormy course, and died five days postoperatively of puerperal infection. Autopsy was not available.

Comment.—This case needs little comment to condemn about every step in her care, from the rupture of the membranes three days before admission, to the repeated vaginal examinations, the failure to diagnose a transverse presentation very much earlier, and the delivery by a classical section. In all fairness it should be said that since this case occurred seventeen years ago the laparotrachelotomy was not in vogue, but there was little excuse for not removing the uterus at the time of operation and in all probability a maternal death would have been avoided.

SUMMARY AND DISCUSSION

From these cases it can be seen that nearly all of the ruptured uteri and maternal deaths were unnecessary tragedies which probably would not have occurred had early diagnosis and proper treatment been the rule in each and every case. If space permitted, close scrutiny of almost every stillbirth in this series from the point of view of preventability would disclose a similar picture.

Careful study of every case leads one to the conviction that a very much lower morbidity and mortality rate would have been attained if certain basic principles had been observed. The most important of these are:

1. The recognition of the transverse or oblique presentation prior to or early in labor.

2. An attempt should be made to correct the presentation of the child by external version.

3. An abdominal binder or a Willett clamp where advisable can often be used to hold the child in its new position.

4. The dangers associated with internal podalic version and breech extraction should be realized and this operation avoided unless all the requirements are present for its proper performance, particularly a fully dilated cervix, lack of disproportion, a sufficient amount of amniotic fluid, and a sound uterus.

5. The more frequent use of the extraperitoneal section and hysterectomy when dealing with infected or potentially infected patients.

6. In the presence of a pelvis which is considerably contracted, particularly in the primipara, the elective cesarean section should be the operation of choice.

7. In certain indicated cases, decapitation is the most advisable procedure.

8. Intelligent antenatal and intranatal care will unquestionably result in the avoidance of many unnecessary fetal and maternal catastrophes which now occur frequently in the hands of those treating the transverse presentation by the method of hopeful expectation.

Blaisdell, Paul C.: Repair of the Incontinent Sphincter Ani, Surg. Gynec. Obst. 70: 692, 1940.

Advantage is taken of a direct attack on the anterior normal portion of the external sphincter rather than on that portion mutilated by operation and deformed by scar tissue, heretofore utilized. A reef is taken in the muscle through the vagina, so that the circumference of the whole muscle and of the anal outlet is diminished. Dependence is placed exclusively on this effect with entire disregard of the scar tissue.

This operation not only largely eliminates the basic sources of failure of the other operations but its advantages are strikingly positive as well: Disruptive infection is avoided in a large proportion of the surgical group by the substitution of clean vaginal approach rather than through the perianal skin. The procedure entirely obviates what is often the most difficult and yet essential step of the usual plastic operation, that is, accurate and adequate identification and dissection of the frayed ends of muscle buried in scar tissue. There are numerous instances in which after repeated clumsy rectal operations the scar tissue occupies such a large part of the anal circumference as to prohibit any possibility of success following removal of the mass. With this operation, on the contrary, the opposing factors of tension and stenosis are entirely controllable. Of course, replacement of over half of the circumference of the anus by scar tissue would impose unsurmountable limitation.

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TREATMENT OF EXPERIMENTAL ANOXIA WITH CERTAIN RESPIRATORY AND CARDIAC STIMULANTS

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THE number of babies which die at birth in the United States approximates 80,000 annually; since an additional 30,000 die during the first day of life, from causes which are almost always natal in origin, the total infant mortality consequent upon the change from intra- to extrauterine life is about 110,000 yearly. The majority of these deaths are respiratory in their clinical picture. Most often, the baby simply does not breathe at birth, despite the fact that the heart is beating and despite attempts at artificial respiration and the use of respiratory stimulants. During recent years, this problem of apnea of the newborn has been attacked with special vigor; several important etiologic factors have been elucidated and various types of therapy suggested. Prominent among the latter are a number of reports recommending the use of medicinal respiratory stimulants, notably, "alpha-lobeline," "metrazol," and "coramine."

Modern interest in alpha-lobeline as a respiratory stimulant dates from 1915 when Wieland of Germany isolated the hydrochloride of lobelia in crystalline form; and subsequently the drug has enjoyed widespread use in such conditions as morphine and chloral poisoning, carbon monoxide asphyxiation, pneumonia, laryngeal stenosis and apnea of the newborn. Metrazol· (pentamethylenetetrazol) and coramine (pyridine-beta-carboxydiethylamide) have also been recommended to combat apnea at birth, both being well known respiratory stimulants. The first published reference to coramine appeared in 1922 under the authorship of Lagier, and since that time almost 1,400 articles have dealt with various aspects of the drug. When employed in apneic newborn, these agents are usually injected directly into the umbilical vein, the dose ranging from one-sixth to one-third the adult dosage.

Although it might seem offhand that the value of alpha-lobeline, metrazol, and coramine in apnea neonatorum could best be determined in actual cases of this disorder, a number of factors renders such clinical observations of dubious reliability. In the first place, many apneic babies cry after thirty seconds or so, even though nothing whatsoever is done to them; naturally, had a drug been given in such cases, the initiation of respiration would have been credited, erroneously, to the therapy. In the second place, the causes of apnea at birth are various, a circumstance which renders the interpretation of treatment difficult. Finally, in the human newborn, rigorous and carefully controlled observations on the effect of any one therapeutic agent are almost impossible, since it is obviously mandatory to employ all recognized means of resuscitation in order to give the infant every possible

chance of survival; consequently drug therapy is often supplemented by other procedures, such as artificial respiration and skin stimulation, thus vitiating any conclusions which might be drawn between cause and effect.

If it is hazardous, then, to draw conclusions from the clinical use of these drugs, what can we say of the experimental approach? From every point of view, the picture of apnea at birth is the picture of anoxia. From a chemical standpoint, the blood is almost depleted of oxygen in the severer examples of this disorder. The variations in the blood oxygen met under various conditions at birth, together with certain other common alterations, are shown diagrammatically in Fig. 1.

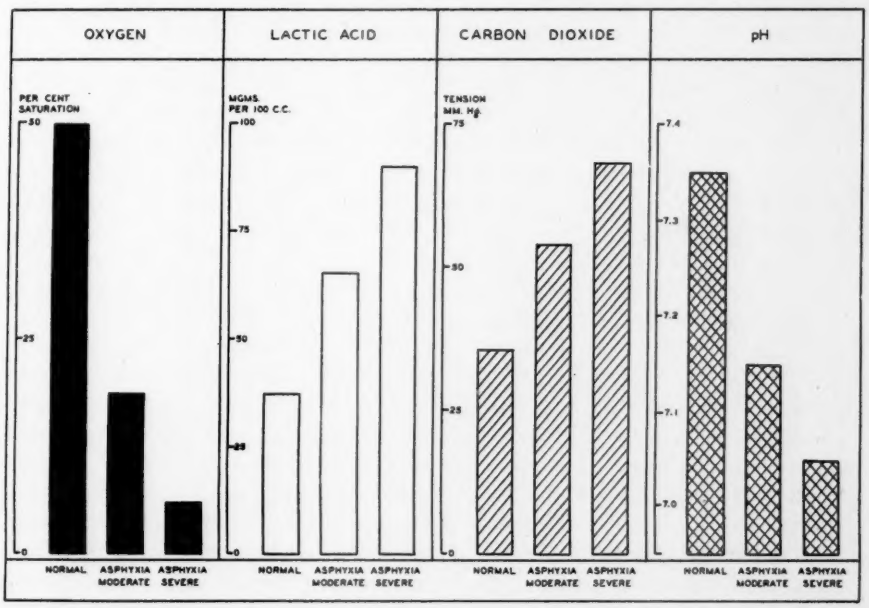

Fig. 1.—Showing the average blood chemical changes in moderate and severe asphyxia neonatorum. It should be noted in particular that the values for carbon dioxide represent the tension or partial gas pressure of free carbon dioxide and not the total carbon dioxide content.

It will be seen that whereas the normal saturation of the arterial blood of the fetus at birth is approximately 50 per cent, in apnea neonatorum the blood oxygen is reduced to levels which represent only one-fifth or even one-tenth of this value. That such low concentrations of oxygen are insufficient for fetal needs is clearly shown by the sharp rise in these cases of blood lactic acid, the characteristic product of anaerobic metabolism in the animal body. Consequent upon the marked increase in lactic acid, the pH of the blood falls to the lowest levels compatible with life. Partly because of an alkali deficit due to fixation of base by lactic acid and partly due to a primary carbon dioxide excess as the result of inadequate diffusion of this gas from fetus to mother, the tension, or partial pressure of free carbonic dioxide, rises to levels far in excess of normal. While these changes in the lactic acid, pH, and carbon dioxide tension of the blood are marked, it should be noted that

they are entirely secondary and that the primary blood chemical change in apnea neonatorum is an extreme reduction in the oxygen content of the infant's blood.

Let us now consider, from the viewpoint of anoxia, the clinical behavior of these apneic babies. Since minor degrees of oxygen want increase the rate and amplitude of respiration, it is often forgotten that profound levels of anoxia (such as we have just described) produce the opposite effect, namely, absence of respiration. And it is seldom recalled in viewing a grave case of asphyxia at birth, with the slow heart rate, the white, cold skin of shock covered with meconium, and the limp extremities, how precisely, how completely this clinical picture duplicates the reaction of any organism to anoxia. In experimental animals, as well as in man, anoxia has been the object of intensive study for over a quarter of a century; on few other subjects has there been such complete agreement, for experimental anoxia produces a constant, clear-cut train of phenomena which may be reduplicated in the laboratory at will. The sequence of events will be recalled as follows. To mild degrees of anoxia the body reacts by increased respiration and accelerated heart rate; these presumably are compensatory mechanisms, the first designed to bring more oxygen to the blood and the second to deliver more oxygen to the tissues. With increasing anoxia, a point is reached when these mechanisms fail to supply oxygen in sufficient amounts for cellular oxidation and then, with remarkable suddenness, "the oxygen crisis" of the physiologists, or what is termed the "reversal" by Schmidt, takes place and after this, events occur rapidly. Consciousness is lost and respirations stop. Following respiratory failure there is an interval of from three to five minutes during which the heart continues to beat; but there is a marked slowing of the rate. In a typical case the slowing occurs in abrupt steps from 150 per minute before the crisis to 44 per minute in the postcrisis phase. After respirations cease, sometimes a little earlier, the blood pressure falls until a systolic level of 15 to 20 mm. Hg is reached. Concomitant with the fall in blood pressure the skin becomes blanched and cold, as in shock. Early in the postcrisis phase of experimental anoxia another important change occurs: the nerve muscle endings of skeletal muscle cease to function with complete collapse of that muscular system. This results, of course, not only in flaccid extremities but in relaxation of the sphincter ani. Finally, it may be noted that a few whiffs of oxygen or air, administered by artificial respiration, restore the animal at once to normal, provided this is done within three or four minutes of cessation of respiration. To summarize the picture of experimental anoxia in the postcrisis phase, there occur in rapid succession loss of consciousness, cessation of respiration, marked slowing of the heart, fall in blood pressure with the white, cold skin of shock, and skeletal muscle collapse, causing general flaccidity of the extremities together with relaxation of the sphincter ani. Surely, few clinical conditions can be simulated so completely as can apnea neonatorum by experimental anoxia.

The close similarity, if not identity, between the severer forms of apnea neonatorum and experimental anoxia made it seem worth while

to study the value of alpha-lobeline, metrazol and coramine in the resuscitation of dogs which had been rendered apneic by anoxia.

METHODS

Dogs weighing between ten and twelve pounds were anesthetized lightly with chloroform and strapped to the table in the usual supine position. The trachea was exposed, opened, and a cannula inserted, through which nitrous oxide-oxygen anesthetic mixtures, and if necessary ether, were administered. Fluctuations in blood pressure were recorded in the usual manner by means of a cannula in the right femoral artery connected with a mercury manometer and slowly revolving kymograph.

Around the animal's chest and upper abdomen was placed a rubber bag which was secured in place by a loosely tied cloth casing. The bladder was inflated slightly and connected to a large tambour by means of a rubber tube, the connecting medium being air. To the rubber membrane was affixed a pointer which recorded the respiratory excursions.

Asphyxiation was accomplished in most experiments by allowing the dog to breathe 100 per cent helium. Because of its well-known ability to penetrate tissues quickly, this inert gas proved superior both to nitrogen and nitrous oxide in its ability to produce rapid and profound anoxia. In a few experiments, 95 per cent helium and 5 per cent carbon dioxide was used as the asphyxiating gas in order to meet the possible objection that the apnea produced was due to a "washing out" of carbon dioxide. The results attained with the latter gas mixture differed in no important way from those achieved by 100 per cent helium.

At the depth of the oxygen crisis blood samples were taken from the left femoral artery for oxygen determination. These showed oxygen levels which ranged between 2.3 and 4.0 volumes per cent; in severe apnea neonatorum, the oxygen levels of the umbilical vein blood vary between 0.5 and 4.0 volumes per cent. All drugs were injected either into the femoral vein or, when stated, into the carotid artery.

RESULTS

Kymographic tracings of the respiration and blood pressure in a typical case of experimental asphyxia are shown in Fig. 2. After thirty seconds of asphyxiation, an increase in the amplitude of respiration may be noted; within another thirty seconds, there is marked hyperpnea for a few breaths, but this is followed promptly by apnea. The fall in blood pressure in this instance is particularly marked. After approximately a minute of apnea, rhythmic insufflations of oxygen restore spontaneous respiration.

To what extent, if at all, may this picture be modified by the injection of alpha-lobeline, metrazol, or coramine?

Fig. 3 shows that alpha-lobeline (3/20 gr.), administered intravenously at the beginning of the apneic phase, exerted no effect whatsoever on the respiration, apnea persisting for a full minute after the drug had been given. It was nevertheless possible to re-establish respiration

within a few seconds by artificial insufflation with oxygen. The temporary rise in blood pressure which followed the administration of the drug in this experiment is very possibly the result of pressor action by alpha-lobeline; but it was not a constant finding and was occasionally

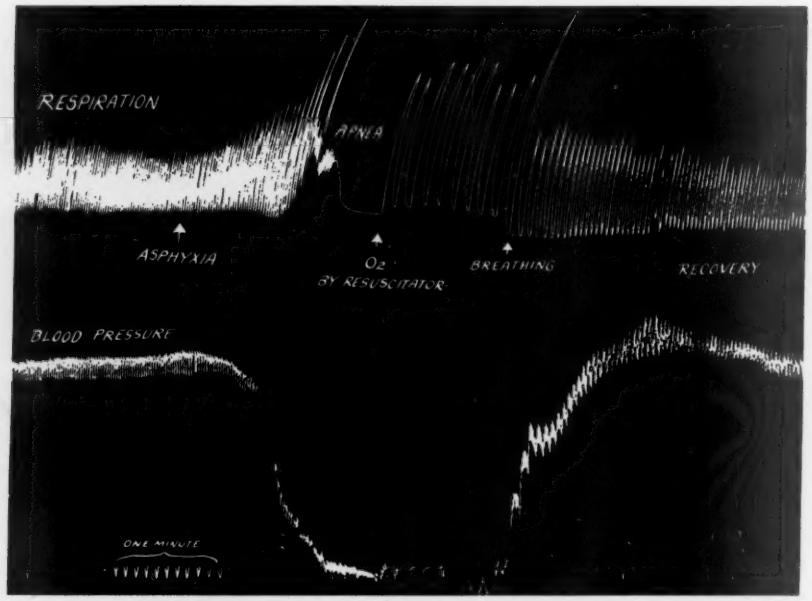

Fig. 2.—Showing behavior of respiration and blood pressure in experimental asphyxia, no stimulating drugs being administered. Resuscitation was effected by insufflation with 100 per cent oxygen as indicated by arrows.

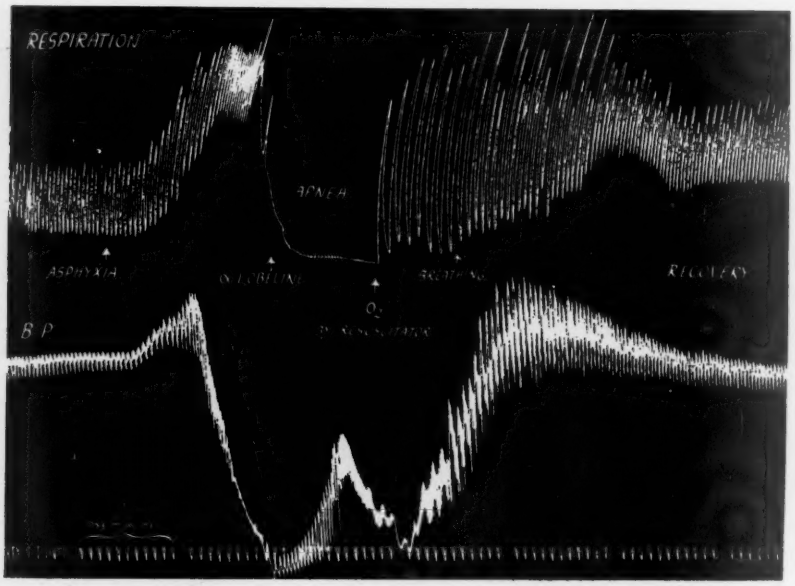

Fig. 3.—Showing failure of alpha-lobeline (3/20 gr. intravenously) to initiate respiration in the presence of anoxia. Breathing was readily established, however, by insufflation with 100 per cent oxygen, as indicated by arrows.

met in experiments in which no drug was given. However this may be, in the presence of continued apnea, the blood pressure quickly returned to its previous low level. The dosage employed in this eighteen-pound dog was the same per kilogram of body weight as that recommended in apneic infants.

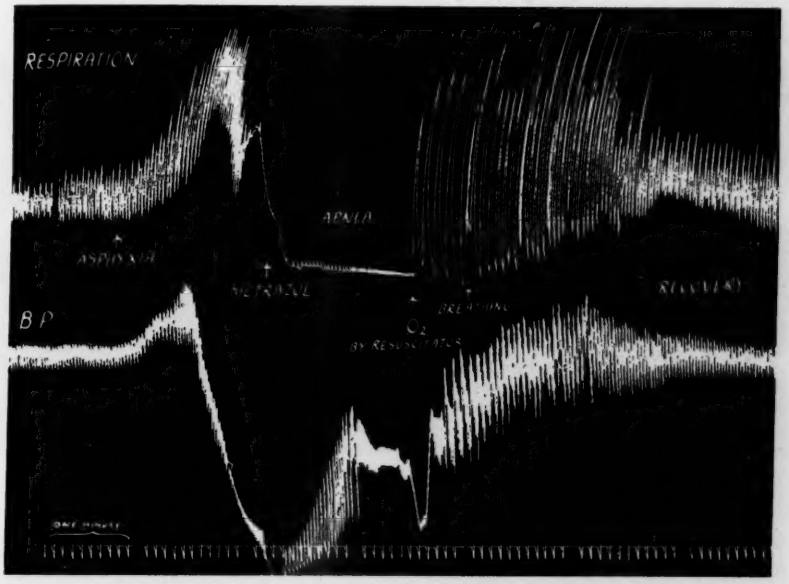

Fig. 4.—Showing failure of metrazol (3 c.c. intravenously) to initiate respiration in the presence of anoxia. Breathing was readily established, however, by insufflation with 100 per cent oxygen, as indicated by arrows.

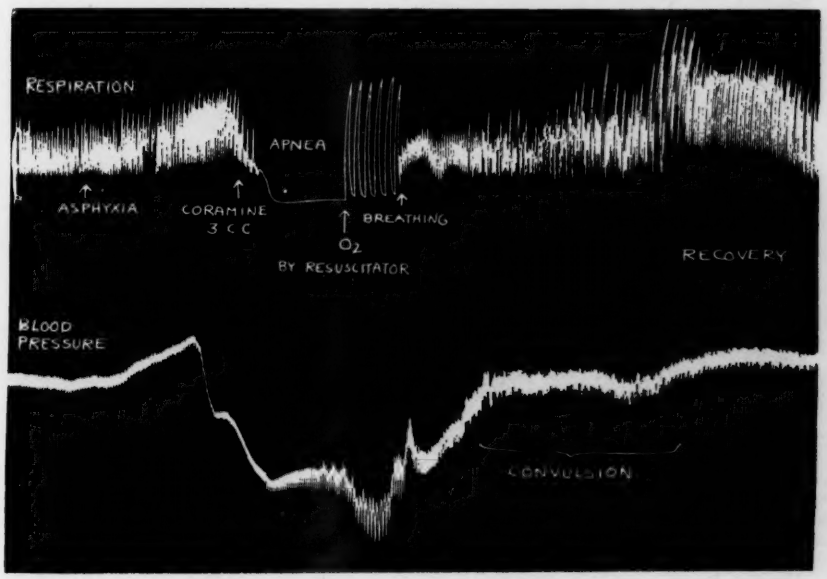

Fig. 5.—Showing failure of coramine (3 c.c. intravenously) to initiate respiration in the presence of anoxia. Breathing was readily established, however, by insufflation with 100 per cent oxygen, as indicated by arrows.

The results in our experiments with metrazol are very similar, a typical example being shown in Fig. 4; metrazol (dosage 3 c.c.) failed to initiate respiration although this could readily be accomplished by insufflation with oxygen. The same temporary rise of blood pressure is observed here as was noted with alpha-lobeline. As may be seen in Fig. 5, our results with coramine were likewise negative, no effect on respiration being observed.

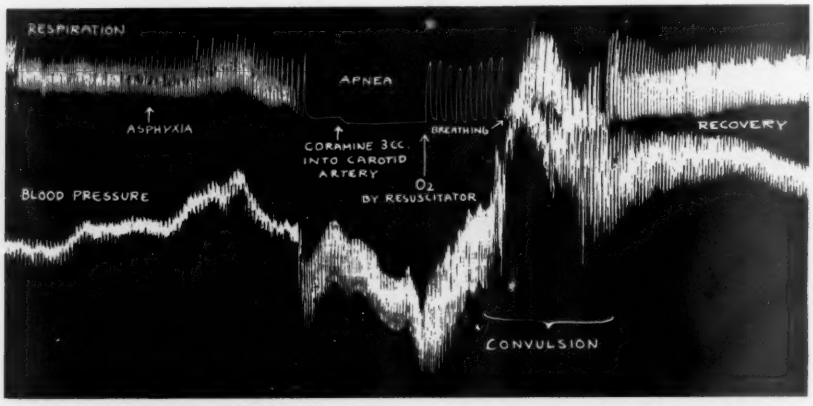

Fig. 6.—Showing failure of coramine (3 c.c.) to initiate respiration even when injected into carotid artery.

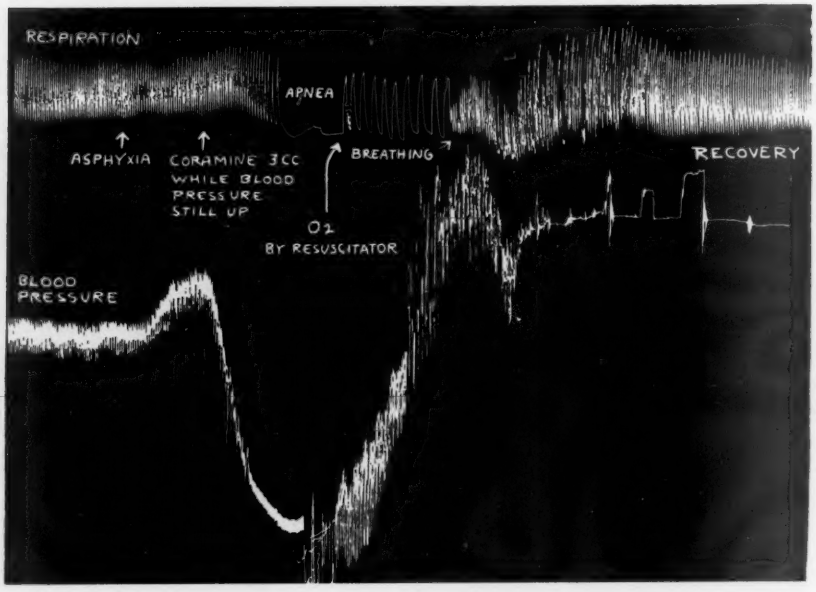

Fig. 7.—Showing failure of coramine (3 c.c. intravenously) to alter the usual picture of experimental asphyxia even when injected at a time when circulation was in good condition.

In all, some 15 such experiments have been carried out with each of these drugs, and in no instance have we been able to detect any effect on respiration in the presence of anoxia.

But it may be objected that these drugs, injected at such low blood pressure levels, did not reach the brain. We have attempted to answer this criticism by injecting each of these drugs, in 3 c.c. of solution, directly into the carotid artery. An example of such an experiment is shown in Fig. 6, and it is readily apparent that the effect on respiration is again nil. Moreover, the same drugs have been injected in the course of asphyxiation but some fifteen or twenty seconds before the blood pressure fell; as shown in Fig. 7, the administration of such a drug, even when the blood pressure is still up, alters in no way the usual pattern of anoxic apnea, the whole train of events proceeding as usual despite the fact that the drug must have made the rounds of the general circulation.

In this series of observations on alpha-lobeline, metrazol, and coramine, convulsions were observed in over one-half of the experiments, but they occurred only after complete re-oxygenation of the blood. Examples of this phenomena are seen in Figs. 5 and 6. The convulsions were of a violent character and lasted from one to two minutes; they were observed following the administration of all three drugs, but occurred more frequently after metrazol. In view of the fact that these drugs are powerful central nervous system stimulants, these findings are not surprising. Indeed, psychiatrists use metrazol therapeutically for the express purpose of producing convulsions, and obstetricians who employ alpha-lobeline in the resuscitation of the newborn report that the babies so treated often exhibit opisthotonos. The fact that in these experiments, however, the convulsions occurred only after the blood had been restored to its normal oxygen content would seem particularly significant, for it can only mean that these drugs, although present in the circulation in convulsive concentrations, are impotent in the presence of anoxia.

It is always hazardous to carry over conclusions drawn from animal experimentation and apply them to clinical therapy. In the present study, moreover, we have ventured to assume that experimentally produced anoxia is identical with the graver types of asphyxia neonatorum. On the basis of the low oxygen shown by these babies, and also on the grounds that the phenomena they exhibit are so very similar to those manifested by animals in anoxic apnea, we believe that there is some justification for this assumption. If this premise is acceptable, it would seem clear that alpha-lobeline, metrazol and coramine have no place in the treatment of apnea at birth because their effect on respiration is nil in the presence of anoxia; and, as we have shown, the severe forms of apnea neonatorum are regularly associated with anoxia. In other words, our findings are in keeping with the viewpoint that the chief desideratum in the treatment of anoxia at birth is not stimulating drugs with their likelihood of convulsive action but, obviously enough, oxygen.

The authors are deeply indebted to Dr. Morris Rosenfeld, of our Department of Pharmacology and Experimental Therapeutics, and to Mr. Edwin Stewart, Jr., for valuable technical assistance.

THE ENDOMETRIUM IN TUBERCULOUS PERITONITIS AND IN STERILITY*

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ENDOMETRIAL tuberculosis is usually regarded as a rare disease. However, it appears to be more common than is generally appreciated. Tuberculosis of the endometrium presents a number of interesting problems from the clinical as well as pathologic aspect, largely because there is no comparable tissue in the body. This is due to the fact that in the normal menstrual cycle the endometrium is constantly changing its histologic appearance until it finally sloughs at the beginning of menstruation.

Our work on this problem includes a careful study of the pathologic changes in the endometriums of 75 uteri which had been removed in the course of surgical procedures. An attempt was made when possible to study recent specimens. Otherwise the cases were taken at random from the files.

REVIEW OF LITERATURE

Very little has been added to the literature concerning uterine tuberculosis since the excellent discussion of Williams in 1893. He expressed the opinion that tuberculosis of the uterus was nearly always secondary to tuberculosis elsewhere in the body and that it was usually associated with tuberculosis of the tubes from which the process extended to the uterus.

According to the statistics offered by various authors, genital tuberculosis has been observed in from 1 to 8.5 per cent of all cases of phthisis, among women, which came to necropsy. In 6,000 routine post-mortem examinations, Simmonds found tuberculosis of the female genital tract in 1.5 per cent of all cases. Williams found 5 cases of unsuspected tuberculosis of tubes and ovaries in the course of 137 laparotomies on women. Miller reported two instances of tuberculosis of the female genital tract in 68 cases in which pelvic laparotomy was performed, an incidence of 2.9 per cent. The exact incidence of tuberculous endometritis is not available because the uterus is not usually removed when no gross involvement is found. According to Jameson, it is probable that in 50 per cent of all cases of genital tuberculosis among women the uterus is involved.

Tuberculosis of the female genital tract appears to be essentially a disease of the childbearing age. Simmonds found that tuberculosis in that region usually occurred between the ages of twenty and forty years. It is extremely rare in children. Kelly in 1901 was able to collect reports of only 21 cases from the literature in which the patient was less than fifteen years of age.

It is generally agreed that evidence of tuberculous peritonitis can frequently be demonstrated when tuberculosis of the uterus and oviducts is present. Schramm, writing in 1882, stated that out of 34 women with genital tuberculosis, 21 had tuberculous peritonitis. Oppenheim noted it in 21 out of 23 cases. Osler stated that the tubes were affected in 30 to 40 per cent of all cases of tuberculous peritonitis.

Kiwisch, Rokitansky, Forster, and Cruveilhier have expressed the opinion that tuberculosis reaches the uterus from the peritoneum by way of the fimbriated end

*Abridgment of thesis submitted by one of us (Jensen) to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

of the tube; they cited as proof the fact that in many cases the process was most marked in the fimbriated portion of the tube and that this was the most vascular portion of the tube as well.

Sterility is not an infrequent accompaniment of tuberculosis of the female genital tract. Greenberg found that in 60 per cent of his series of 200 cases of tubal tuberculosis there was a clinical history of sterility. He found that the uterine mucous membrane was involved in 45 per cent of the cases in which tuberculosis of the Fallopian tube was present.

Williams in routine histologic examinations noted that adnexitis was tuberculous in 8 per cent of all cases. The uterus was involved in 60 to 75 per cent and the ovaries in 40 to 45 per cent of the cases in which the tubes were tuberculous. Norris claimed that pre-existing inflammatory lesions apparently predisposed to the development of tuberculous salpingitis. In about one-third of his cases of tubal tuberculosis, another form of salpingitis preceded. He also claimed the puerperal state to be a predisposing factor. Granzow from animal experimentation found that pregnancy and especially the puerperium increased the general susceptibility of the genital tract to infection with tuberculosis.

METHOD OF STUDY

The 75 uteri which were chosen for this study were classed into three groups. The first group consisted of 25 uteri which had been removed surgically from women who had borne children and who were not suspected of having tuberculosis before operation. The second group consisted of 25 uteri surgically removed from women who had never borne children in spite of the fact that they were married and desired to have children. Tuberculosis was not suspected preoperatively in any of these cases. The third group contained uteri from women who had tuberculosis of the peritoneum which was verified by histologic examination. Hysterectomy was performed either at the time of the diagnosis of the tuberculous peritonitis or at a subsequent date.

In all cases one block of tissue was taken from each of four different locations in the uterine mucous membrane: right horn, left horn, mid-uterus (the wall halfway between fundus and cervix), and endocervix. A portion of the myometrium together with the full depth of the endometrium or endocervix was included in each block. Sections were made from each block of tissue and stained with hematoxylin and eosin. The blocks were of approximately the same size and generally two sections from each block were examined microscopically. The histologic presence of a tubercle containing the characteristic epithelioid cells with or without necrosis was considered sufficient for a positive diagnosis of tuberculosis. Foreign body giant cells or lymphocytes were not considered essential to the diagnosis of tuberculosis.

The involvement of endometrium and endocervix was graded as follows: Involvement was classified as of Grade 1 when a total of 1 to 2 tubercles were found in the sections examined; Grade 2 when there were 3 to 6 tubercles; Grade 3 when there were 7 to 12 tubercles present; and Grade 4 when more than 12 tubercles were present. In addition to the number of tubercles, other factors were taken into consideration, such as the number of sections involved, the location, spread and extent of the tuberculosis as well as the presence or absence of caseation.

Attempts have been made by various authors to classify the pathologic features of genital tuberculosis into several groups, such as

miliary tuberculosis with or without formation of ulcerations, chronic diffuse tuberculosis and chronic fibroid tuberculosis; others have mentioned the ulcerocaseous, hypertrophic, and interstitial forms. Such classifications are based on the gross appearance and are of little or no practical importance from a clinical standpoint. No attempt was made in this series to classify tuberculosis into these groups.

RESULTS

Group 1. Tuberculous Endometritis Among Parous Women.—In one specimen from this group of 25 uteri, tuberculosis was found in the block of endometrium taken from the midportion of the uterus. Only two tubercles were found. In this case also there was bilateral involvement of the oviducts and of the left ovary, but the cervix was not involved.

Group 2. Tuberculosis of the Endometrium Among Sterile Women.—Among the 25 cases of primary sterility in which hysterectomy had been performed were 2 cases in which tuberculosis of the uterine mucous membrane was found on microscopic examination of the endometrium and endocervix. In both cases bilateral tuberculous salpingitis was present also. In one only, endocervical tuberculosis was found; in the other case only the endometrium was involved in the region of the right horn. In this latter case only 2 out of 4 sections from the same block revealed involvement. The reason for removal of the uterus in both cases was the presence of multiple fibromyomas. The tuberculosis was unsuspected on clinical examination. In both cases the involvement was only minimal.

There was no involvement of the myometrium or of the basal glands and no caseation of the tubercles in this group (Table I).

TABLE I. TUBERCULOSIS OF THE ENDOMETRIUM IN 25 CASES OF STERILITY (GROUP 2)

NO.	LOCATION OF TUBERCULOSIS	ENDOCERVIX		ENDOMETRIUM		BASAL GLANDS INVOLVED	GRADE OF INVOLVEMENT	CASEATION	REMARKS
		MUSCLE	MUCOSA	MUSCLE	ENDOMETRIUM				
1	Endocervix only	0	+	0	0	0	1	0	Only 2 of 4 sections in same block contained tubercles
2	Right horn	0	0	0	+	0	1	0	Minimal

Group 3. The Endometrium in Tuberculous Peritonitis.—The third and final group of 25 cases includes all the cases of proved tuberculous peritonitis, in which the uterus was removed at the time of the diagnosis or subsequently at the Mayo Clinic. Of these 25 cases, tuberculous endometritis was demonstrated in 15, or 60 per cent (Table II; Figs. 1, 2, and 3). The only examples of caseation found in the entire series were in this group. Endocervical involvement occurred in 47 per cent of the cases. In all 15 cases the oviducts were tuberculous. In one case tuberculosis and adenocarcinoma Grade 1 of the cervix were present.

When the 18 cases of tuberculosis from the three groups are considered, in 14 there was involvement of the endometrium and in 7 involvement of the endocervical mucosa.

COMMENT

In the experimental production of tuberculosis, caseation does not appear in the tubercles in its early stages.[8] However, the absence of caseation in tuberculosis does not necessarily prove that a given lesion is early, since tuberculosis can be demonstrated especially in lymphoid tissue, the lymph nodes and tonsils, in which there is a minimal amount

TABLE II. TUBERCULOSIS OF THE ENDOMETRIUM IN 25 CASES OF TUBERCULOUS PERITONITIS (GROUP 3)

NO.	LOCATION OF TUBERCULOSIS	ENDOCERVIX		ENDOMETRIUM		BASAL GLANDS INVOLVED	GRADE OF INVOLVEMENT*	CASEATION	REMARKS
		MUSCLE	MUCOSA	MUSCLE	ENDOMETRIUM				
1	All involved	+	+	+	+	+	4	+	Tuberculosis evident in all sections
2	All involved	+	+	+	+	+	4	0	Extensive tuberculosis
3	All involved	0	+	+	+	+	4	+	Only 1 tubercle noted in endocervix
4	All involved	+	+	0	+	0	4	0	Marked involvement of endocervix, others less
5	Both horns and mid-uterus	0	0	0	+	+	3	0	
6	Endocervix only	+	+	0	0	0	3	0	Many tubercles found
7	Both horns and mid-uterus	0	0	0	+	0	2	0	On routine sections only one suspicious area found
8	Mid-uterus	0	0	0	+	0	2	0	Tubercles found in one section only
9	Right horn	0	0	0	+	0	2	0	Tubercles found in one section only
10	Right horn	0	0	0	+	0	1	0	One tubercle only
11	Endocervix and mid-uterus	+	0	+	0	0	1	0	Tubercles seen in muscle only
12	Left horn	0	0	0	+	0	1	0	1 tubercle seen in 10 sections
13	Left horn	0	0	0	+	0	1	0	
14	Endometrium	0	0	0	+	0	1	0	
15	Endocervix only	0	+	0	0	0	1	0	

*Grading on basis of 1 to 4 in which 1 is slight and 4 extensive involvement.

of caseation and yet the lesion may be of many years' duration. In the present study caseation was seldom found in the endometrium or the myometrium. Furthermore the tubercles in this series were encountered most frequently in the superficial layers of the endometrium, less commonly in the basal layer and the myometrium. The endometrium is the only tissue in the body which is shed at regular intervals during premenopausal adult life. For this reason tubercles in the superficial

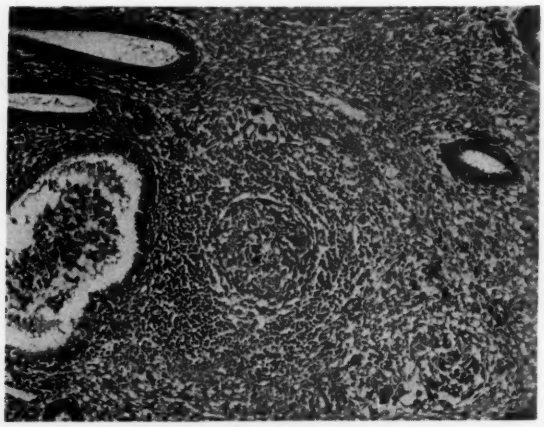

Fig. 1.—Tuberculosis of the endometrium. One tubercle is shown (hematoxylin and eosin, ×110).

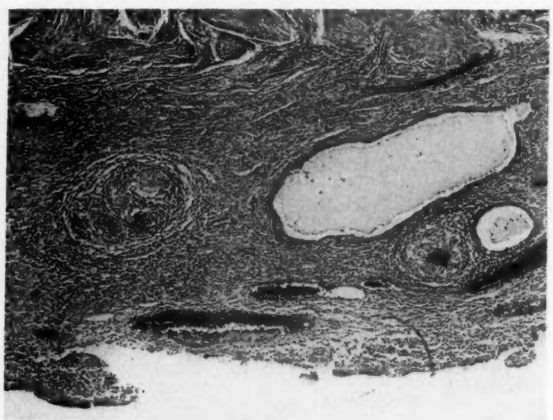

Fig. 2.—Tuberculosis of the endocervix showing two tubercles (hematoxylin and eosin, ×55).

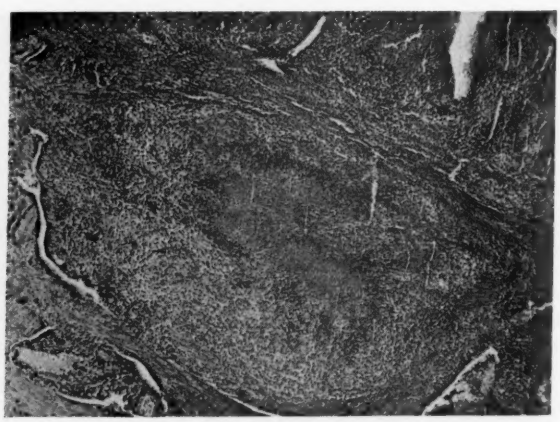

Fig. 3.—Tuberculosis of the endometrium. An area of caseation is seen (hematoxylin and eosin, ×55).

layers of the endometrium are young, less than a month old. This no doubt partly accounts for the lack of caseation in this location. On the other hand tubercles when present in the myometrium and endocervix rarely show caseation in spite of the fact that neither of these structures is sloughed. This suggests an inherent capacity of the uterus to resist caseation. On the other hand, in 2 cases in which caseation was present in this group, there was a widespread involvement of practically all the structures in the uterus. This would suggest that when caseous tuberculosis is found in a specimen obtained at curettage, radical surgical treatment should be advised, because the process is likely to be extensive in the uterus.

It is also significant that tuberculosis was frequently not evident in most of the sections and that out of many sections from different parts of the endometrium and endocervix only one or two might give the pathologic picture of tuberculosis. In most instances the diagnosis of tuberculosis of the uterus is made on microscopic examination.

Tuberculosis appears to manifest itself primarily in the oviducts. In every case in which tuberculosis was demonstrated in the endometrium in this series there was tuberculous involvement of the oviducts. Hence, a diagnosis of tuberculous endometritis could have been considered tantamount, with few exceptions, to a diagnosis of bilateral tubal tuberculosis. This agrees with the opinion expressed by Norris and others. On the other hand tuberculous salpingitis does not necessarily imply that the endometrium is infected. In this series, the endometrium was involved in 60 per cent of cases in which tuberculous salpingitis was present. It seems likely that this figure would be higher if more exhaustive studies of the endometrium were made.

One of the most important considerations in genital tuberculosis is the site of involvement of the uterus. Obviously the condition in the uterus is not as serious when only the endometrium is involved as it is when the basal glands or the myometrial or endocervical tissues, which do not slough off at the time of the menstrual period are involved; in such cases, the probabilities of extension are much greater, the tuberculosis is of a more serious nature and is less likely to be controlled by conservative methods. When the endometrium is extensively involved, the myometrium almost always shows evidence of tuberculosis.

With the monthly desquamation of the endometrium, the question may well be raised as to why patients with tuberculous endometritis do not develop tuberculosis of the vagina or external genitalia. We found no instance of this in our series. It has been noted that in the experimental production of genital tuberculosis in guinea pigs, lesions of the vagina and external genitalia were uncommon, even following inoculation.

Tubercles on the serosal surface of the uterus are not necessarily a sign of tuberculosis of the uterus, but rather are evidence of tuberculous peritonitis.

An interesting finding in this group was the frequency of tuberculosis of the endocervical mucosa, often with extension to the musculature. In 7 cases, tuberculous lesions of the endocervix, cervical muscle,

or both were found. Since the mucosa in this situation remains fixed, this might well serve as a source for the continuation of the infection. Endocervical tuberculosis has not received the attention that should be accorded it. In 2 cases in this series the endocervix only was involved.

SUMMARY AND CONCLUSIONS

In 2, or 8 per cent, of 25 cases of sterility studied, tuberculosis of the uterus was encountered.

The incidence of tuberculous endometritis in the 25 uteri from parous women studied was 4 per cent. However, in the 25 cases of tuberculous peritonitis studied, in which the uterus was surgically removed, tuberculous involvement of the uterus was found in 60 per cent.

Endocervical tuberculosis was found more frequently than has been described previously. It seems likely, therefore, that if more extensive histologic study were made of the endometrium in routine curettings and hysterectomies, the incidence of tuberculosis of the uterus would be found to be much higher.

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THE CONTRACTILE RESPONSE OF THE PREGNANT HUMAN UTERUS TO POSTERIOR PITUITARY EXTRACT

A Study of 375 Injections Recorded With the Lóránd Tocograph

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IT IS well known that the uteri of pregnant women vary widely in their contractile responses to the administration of oxytocic drugs. There may be: (a) no response, (b) the inauguration of clonic contractions, or the augmentation of pre-existing ones, (c) a tetanic spasm, or (d) a combination of tetanic and clonic contractions. A tetanic reaction may be so intense and prolonged as to cause fetal death or even rupture of the uterus.

The unpredictability of the uterine reaction, and the seriousness of severe tetanic spasms indicate the need for more knowledge regarding the conditions under which untoward reactions are most likely to be observed. The advent of the Lóránd tocograph,[1-4] which affords, to a certain extent at least, a quantitative as well as a qualitative measure

of the contractile reaction of the pregnant uterus, affords a means for studying certain of the factors which modify the drug action.

The present study deals directly with the power of posterior pituitary extract to induce or modify the contractions of the uterus which take place during pregnancy and labor, and indirectly with certain factors which have a tendency to modify the contractile response. The object of the report is to indicate which of the factors studied are likely to lead to an unsatisfactory type of reaction. Such knowledge may be an aid in improving the results achieved when posterior pituitary extract is employed for the purpose of either inducing labor or improving the character of existing contractions.

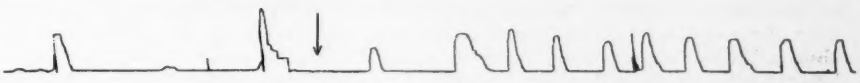

Fig. 1.—Tracing 245. Tocographic record of uterine contractions. One minim of pitocin administered hypodermically at arrow. Note increase in frequency of contraction waves without elevation of the base of the waves. Typical clonic response.

Fig. 2.—Tracing 256. Tocographic record of uterine contractions. One minim of pitocin administered hypodermically at arrow. Note increased frequency of contractions accompanied by temporary elevation of the base of the waves. Typical incomplete tetanic response.

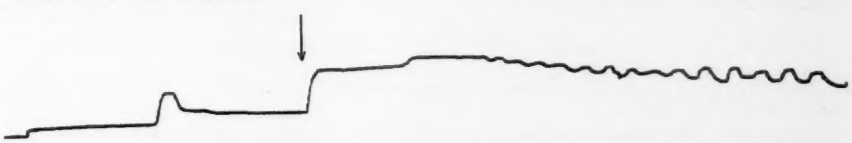

Fig. 3.—Tracing 956. Tocographic record of uterine contractions. One cubic centimeter of pitocin administered hypodermically at arrow. Note prolonged elevation of what would have been the wave base, if any had been present, together with obliteration of any signs of intermittent contractions for some time. Typical complete tetanic response.

MATERIALS AND METHODS

Patients attending the Maternity Department of the Hospital of the University of Pennsylvania and ones living at the Sheltering Arms Home acted as subjects. They were observed between March 22, 1939, and June 6, 1940. Each woman received one or more hypodermic injections of either obstetric pituitrin or pitocin (Parke, Davis & Co.) before, or during labor, or both. The resulting uterine contractions were recorded by means of a Lóránd tocograph. This is a simple mechanical device[2] for registering the movements of the pregnant uterus through the medium of the anterior abdominal wall, upon a strip of paper. The tocographic record was begun fifteen minutes or more before the injection, and was continued for at least thirty minutes thereafter. The contractile response was then analyzed with respect to the influence upon it of the following conditions: (1) parity, (2) the time in pregnancy that the treatment was given, (3) dosage, (4) the tension of the uterine wall.

Definitions.—A positive response is said to have occurred if a clear-cut alteration in the tocographic record took place within fifteen minutes of treatment time, which could not be charged to any other cause. Positive responses are classified as being clonic or tetanic, and if tetanic, as being either incomplete or complete.

A clonic response is indicated by the occurrence of rhythmically recurring waves inaugurated or augmented by treatment, without coincident elevation of the level of the valleys between the waves.

A tetanic response is characterized by an elevation of the recording line for a longer period than is required by a single clonic contraction. It is classified as being *incomplete* if it fails to interrupt the rhythm of the clonic contractions, and *complete* if one or more of these contractions do not occur. Examples of these responses appear in Figs. 1 to 3 inclusive.

Tension of Uterine Wall.—The tension of the uterine wall is measured in the following way: The tocograph is laid upon the most prominent part of the pregnant abdomen, with the patient supine. Early in pregnancy when the uterus is soft to the touch, and the tension of the uterine wall is low, the recording button on the bottom of the tocograph, which is in direct contact with the abdomen, meets no appreciable resistance from the underlying uterus, and consequently fails to displace the recording pen as the record is being made. If, on the other hand, the observation is made when the uterus is more tense, it displaces the recording button into the tocograph and thus changes the position of the recording pen upon the moving paper strip. Under the former conditions, for the sake of convenience, the uterus is said to exhibit no increase in the tension of its wall, whereas in the latter situation an increase in tension is said to exist. Furthermore, the degree of displacement of the writing pen appears to be proportionate to the degree of tension present.

RESULTS

A series of 96 patients, of whom 44 were multigravidas, received 375 hypodermic injections of obstetric pituitrin (291 treatments), or pitocin (84 treatments). Three hundred and forty-one treatments were given before, and 34 during labor. The dosages in minims were as follows: 0.5, 1.0, 1.5, 2.0, and 3.0. The number of observations per person is shown in Table I.

TABLE I. TREATMENTS PER PATIENT

Showing number of hypodermic injections of either obstetric pituitrin or pitocin received by each patient.

NUMBER		NUMBER	
TREATMENTS	PERSONS	TREATMENTS	PERSONS
1	42	10	2
2	14	11	2
3	7	12	2
4	4	13	1
5	5	14	0
6	4	15	1
7	6	24	1
8	2	25	1
9	2		
		Total	96

Incidence and Character of Response.—Of the 375 treatments (Table II), only 200 (53 per cent) elicited a positive response. Of the latter, 127 (63 per cent) were clonic, and 73 (37 per cent) tetanic. Of the tetanic ones, 23 were of the complete variety, being 11.5 per cent of all positive responses.

Parity.—Primigravidas responded less often than multigravidas, in the ratio of 46 to 77 (Table II), and their percentage of tetanic responses was higher (ratio of 39 to 31).

Labor.—Responses were more common *during* than before labor in the ratio of 76 to 51 (Table III), but *complete* tetanic responses were more common *before* than during labor in the proportion of 33 to 22.

TABLE II. INFLUENCE OF PARITY UPON RESPONSE

Showing influence of parity upon uterine contractile response to posterior pituitary extract. Note: (1) Higher response rate in multigravidas, (2) greater frequency of tetanic responses among primigravidas.

RESPONSE	PARITY				TOTAL	
	PRIMIGRAVIDAS		MULTIGRAVIDAS			
	TREATMENTS					
	NO.	%	NO.	%	NO.	%
I Frequency:						
Treatments	284	100	91	100	375	100
Responses	130	46	70	77	200	53
II Types:						
Clonic	79	61	48	69	127	63
Tetanic	51	39	22	31	73	37
	130	100	70	100	200	100
III Tetanic:						
Incomplete	35	69	15	68	50	69
Complete	16	31	7	32	23	31
	51	100	22	100	73	100

TABLE III. INFLUENCE OF LABOR UPON RESPONSE

Showing influence of existence of labor upon uterine contractile response to posterior pituitary extract.

Note: (1) Higher response rate during labor than before, and (2) higher incidence of complete tetanic responses before than during labor.

RESPONSE	TREATMENT TIME IN RELATION TO LABOR				TOTAL	
	BEFORE		DURING			
	TREATMENTS					
	NO.	%	NO.	%	NO	%
I Frequency:						
Treatments	341	100	34	100	375	100
Response	174	51	26	76	200	53
II Type:						
Clonic	110	63	17	65	127	63
Tetanic	64	37	9	35	73	37
	174	100	26	100	200	100
III Tetanic:						
Incomplete	43	67	7	78	50	69
Complete	21	33	2	22	23	31
	64	100	9	100	73	100

Duration of Pregnancy.—Irrespective of the dosages employed, no response was elicited prior to the seventh lunar month (Table IV); from then on the frequency increased progressively as pregnancy advanced; coincidentally the incidence of tetanic response decreased.

Dosage.—The influence of dosage was studied in the patients who were treated during the tenth month (Table V). All responses and tetanic ones alone were both more common following the larger doses.

Uterine Wall Tension.—The influence of uterine wall tension upon response in those patients observed during the tenth month of gestation is shown in Table VI. Responses were observed when there was an increase in uterine tension, twice as often as in its absence. Tetanic reactions also were more common in the presence of an increase in tension.

TABLE IV. INFLUENCE OF DURATION OF PREGNANCY UPON RESPONSE

Showing influence of duration of pregnancy upon the uterine contractile response to posterior pituitary extract. Note: Greater response frequency late in pregnancy.

RESPONSE	DURATION OF PREGNANCY IN MONTHS														TOTAL	
	4		5		6		7		8		9		10			
	TREATMENTS															
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
I Frequency:																
Treatment	1	100	8	100	8	100	19	100	46	100	83	100	176	100	341	100
Response	0	0	0	0	0	0	4	21	12	26	41	49	117	66	174	51
II Type:																
Clonic	0	0	0	0	0	0	4	100	5	42	24	59	77	66	110	63
Tetanic	0	0	0	0	0	0	0	0	7	58	17	41	40	34	64	37
	0	0	0	0	0	0	4	100	12	100	41	100	117	100	174	100
III Tetanic:																
Incomplete	0	0	0	0	0	0	0	0	6	86	11	65	26	65	43	67
Complete	0	0	0	0	0	0	0	0	1	14	6	35	14	35	21	33
	0	0	0	0	0	0	0	0	7	100	17	100	40	100	64	100

TABLE V. INFLUENCE OF DOSAGE UPON RESPONSE DURING TENTH MONTH

Showing influence of dosage administered during tenth month of pregnancy upon uterine contractile response to posterior pituitary extract. Note: (1) Greater response frequency after larger doses, and (2) greater tetanic response frequency after larger doses.

RESPONSE	DOSAGE IN MINIMS										TOTAL	
	0.5		1.0		1.5		2.0		3.0			
	TREATMENTS											
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
I Frequency:												
Treatments	9	100	57	100	29	100	48	100	32	100	175	100
Responses	8	89	28	49	21	73	37	77	23	72	117	67
II Types:												
Clonic	8	100	22	79	11	52	26	70	11	48	78	67
Tetanic	0	0	6	21	10	48	11	30	12	52	39	33
	8	100	28	100	21	100	37	100	23	100	117	100
III Tetanic:												
Incomplete	0	0	3	50	8	80	6	55	9	75	26	67
Complete	0	0	3	50	2	20	5	45	3	25	13	33
	0	0	6	100	10	100	11	100	12	100	39	100

DISCUSSION

The present data confirm the observations of many clinicians that uterine response does not always follow the administration of posterior pituitary extract during pregnancy. Using doses of 3 minims or less we observed no contractile response after 47 per cent of treatments.

On the other hand, even using these small doses, we observed a tetanic type of reaction following in approximately 37 per cent of treatments which exhibited any response whatever. In 11.5 per cent of instances the tetanus was of such a degree as to obscure any evidence of clonic activity (complete tetanic response). It is apparent, therefore,

TABLE VI. INFLUENCE OF UTERINE WALL TENSION UPON RESPONSE DURING TENTH MONTH

Showing influence of uterine wall tension upon uterine contractile response to posterior pituitary extract. Note: (1) Greater response frequency in presence of increased uterine wall tension, (2) greater frequency of tetanic contractile reactions in presence of increased uterine wall tension, and (3) greater frequency of complete tetanic contractile reactions in presence of increased uterine wall tension.

RESPONSE	UTERINE WALL TENSION				TOTAL	
	NOT INCREASED		INCREASED			
	TREATMENTS					
	NO.	%	NO.	%	NO.	%
I Frequency:						
Treatment	111	100	64	100	175	100
Response	54	49	63	98	117	67
II Type:						
Clonic	51	94	27	43	78	67
Tetanic	3	6	36	57	39	33
	54	100	63	100	117	100
III Tetanic						
Incomplete	3	100	23	64	26	67
Complete	0	0	13	36	13	33
	3	100	36	100	39	100

that even following the administration of small doses of the extract the pregnant uterus is likely to experience a tetanic reaction. This is an important fact to bear in mind when administering posterior pituitary extract to a pregnant woman.

TABLE VII. SUMMARY OF DATA IN TABLES II TO VI (INCLUSIVE)

Summary of the effects of the factors described in more detail in Tables II to VI inclusive. Note: (1) How all factors increase the percentage of responses to posterior pituitary extract, (2) that increase of dosage and increase in tension of the uterine wall increase the percentage of tetanic response, and (3) that the increase in tension alone increases the percentage of complete tetanic responses.

FACTOR INFLUENCING RESPONSE	EFFECT UPON		
	RESPONSE FREQUENCY	TETANIC RESPONSE FREQUENCY	
		COMPLETE AND INCOMPLETE	COMPLETE
Multiparity	×*	–*	–
Labor	×	–	–
Advancing pregnancy	×	–	–
Increase of dosage	×	×	–
Increase of uterine wall tension	×	×	×

×, Increase in response frequency.
–, No increase.

The data summarized in Table VII indicate the relative importance of the factors we have investigated. The two important ones are dosage and uterine wall tension because of the rôle they play in bringing about a tetanic type of reaction. The tension of the uterine wall appears to be the more important of the two. Not only does an increase in uterine wall tension increase the frequency of tetanic activity, but it also increases the chance that the tetanic contraction will be of the complete type.

For a long time it has been known that large amounts of posterior pituitary extract may have serious consequences for either mother or child when employed during labor, but little if any attention has been directed to the part played by the existence of a high uterine wall tension in bringing about such unfortunate results. The present study emphasizes this point. Personal unpublished observations indicate that an oxytocic drug administered to a patient exhibiting a high uterine wall tension has little effective value in either inducing or augmenting clonic activity. Under such conditions the uterine muscle is already so much contracted that there exists little opportunity for further contraction—at least of the clonic variety. Consequently, when a patient possessing such a uterus receives a dose of an oxytocic drug, the result is likely to be a further tightening of the uterus to such a degree that any clonic activity is impossible. It follows from this that the effectiveness of an oxytocic drug is useful in proportion to the degree of relaxation exhibited by the uterus, and that if it is administered in the presence of a high degree of uterine wall tension, no good and perhaps harm may result. From this study, it would seem then that the obstetrician should utilize extremely small doses of posterior pituitary extract at all times, using small doses more often, rather than larger ones less frequently; that the tension of the uterine wall should be a guide in deciding whether or not to use the drug, and certainly if the tension is increased considerably, the dose, if given at all, should be extremely small. A subsequent study will deal with the question of uterine wall tension in greater detail, and the conditions under which it is most likely to appear.

SUMMARY

1. A series of 96 women at various stages of pregnancy and labor received 375 hypodermic injections of posterior pituitary extract not exceeding 3 minims per dose. During treatment a continuous record was made of their uterine contractions with a Lóránd tocograph.

2. Forty-seven per cent of treatments elicited no uterine response.

3. An increased frequency of response was noted more often: (a) in multigravidas than in primigravidas, (b) during than before labor, (c) later in pregnancy than earlier, (d) after the larger than the smaller doses of pituitary extract, and (e) when the uterine wall was tense than when it was relaxed.

4. The tetanic type of response occurred most often: (a) when the dose was large, and (b) when the uterine wall tension was high.

5. Complete tetanic contractions occurred most often: (a) when the uterine wall tension was high.

6. From this study the following conclusions are drawn: (a) That the amount of posterior pituitary extract employed, and the degree of tension of the uterine wall at the time of treatment, are two important factors to be considered when attempting to avoid an unsatisfactory type of uterine contraction during pregnancy and labor. (b) That during pregnancy and labor the most efficient type of uterine contraction is produced by the administration of small doses of pituitary extract. (c) That whether or not the drug should be employed, and how

much should be used, during pregnancy or labor should not be decided without considering the degree of tension of the uterine wall.

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LOCAL REFRIGERATION IN GENITAL CANCER*

A REPORT OF TEN CASES

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THE work of Smith and Fay,[1, 2] in refrigeration of cancer patients deserves attention, since their investigations covered a fair amount of clinical material and were supported by laboratory experiments and biopsy material which showed regressive cell changes. The idea had grown out of their observations on the effects of lowered temperatures on the rate of growth in plant and animal life. Freezing was found to be safe, for if the temperature was later raised to a normal level, growth was resumed unaltered. However, if low temperatures were maintained, cells were found to die, or degenerate, or produce cells which could not survive. Normal cells were said to survive a lower subnormal temperature than tumor cells, thus permitting the application of refrigeration for therapy. Pain was promptly relieved and the size of the tumor reduced.

A large number of women are admitted to Kings County Hospital with genital cancer so advanced that, except for relief of pain and nursing care, there is little to be done for them. For this reason we were desirous of giving refrigeration a trial. It appeared to us that for women with advanced pelvic carcinoma, particularly those who had been more or less completely irradiated elsewhere, any therapeutic measure which might possibly improve their status, or even relieve their pain, deserved serious consideration.

Local refrigeration was begun in November, 1939, with the intention of adding general refrigeration later. Our first equipment was a water pump which drove water through a metal coil immersed in a solution of salt and ice, then through rubber tubing into a hollow metal applicator designed and shaped to cover the lesion as completely as possible. Flow was continuous and temperatures were fairly well maintained by constant attention to the ice and brine solution. A little later very satisfactory equipment with automatically controlled temperature was generously loaned to us.† Applicators were devised by us to meet various conditions.

*Read at a meeting of the Brooklyn Gynecological Society, October 4, 1940.

†Wallace and Tiernan Products Incorporated, Belleville, N. J.

In all, 10 patients received local refrigeration. There were 9 cases of cancer of the cervix, and 1 of cancer of the vulva. The majority of the patients had received maximal irradiation; the lesions were extensive and advanced, and secondary infection was marked in every case. In 4 of these cases, local refrigeration was discontinued after trial of six to twelve hours, because of the patient's failure to cooperate or her refusal to continue treatment. In the other 6 patients, local refrigeration was continued for 120 to 900 hours. Serial biopsies were studied. A report of these 6 cases follows:

CASE REPORTS

CASE 1.—A. J., white, single, aged 55 years, was admitted on Dec. 7, 1939, for a highly malignant carcinoma of the cervix; supravaginal hysterectomy had been performed thirteen years before. The cervix was very large with a deep central crater, and the parametria were thick, hard, and nodular. Biopsy of the cervix showed a plexiform anaplastic malignant growth comprised of sheaths of oval and polyhedral cells varying markedly in size and shape; cytoplasm was scant, the deeply hyperchromatic nuclei occupying the greater part of the cells; infection was present.

Local refrigeration was begun on December 9, and continued until January 17, at a temperature of 50° F. On January 11 moderate reduction in size of the mass was observed, and on January 20 she signed her release from the hospital. The mass had become much smaller, and pain had been somewhat relieved. She is known to have died at home three weeks later.

In the biopsy of December 21, cellular changes were first observed. Cytoplasm showed hyperchromatic degeneration, with poorly staining nuclei and indistinct cell outlines; mild necrosis was seen. On December 26, many broad areas and large vacuoles were seen, but no nuclei; vacuolization of cytoplasm was common, nuclei were swollen and poorly stained, and karyorrhexis was observed. In the biopsy of January 17, these changes were the most marked. Hydropic degeneration of cells and absence of nuclei were commonly noted.

CASE 2.—A. M., white, widow, aged 75 years, was admitted on Dec. 10, 1939, for extensive epidermoid carcinoma of the vulva. She had previously received 60 roentgen treatments. The labia and lower vagina were tightly distended by an irregular cartilaginous-like growth; the labia were fissured in several places, and foul purulent exudate exuded. Biopsy showed epidermoid carcinoma with small spindle cells and polyhedral cells invading the entire corium; narrow cords, large islands and invaginating papillary processes of squamous epithelial cells with keralinization and pearl formation were seen. The scant stroma showed extensive exudate and infection.

On December 14, refrigeration was begun with a combined vaginal and vulvar applicator. A temperature of 50° F. was maintained until Jan. 9, 1940. On December 17, swelling and induration had diminished and pain was relieved. Treatment was discontinued when oral temperature fell to 94° F., and she became drowsy; blood urea was 31 mg. per cent. She declined steadily and died in coma on Jan. 27, 1940.

Slight destructive changes were first noted in the biopsy of January 17. Biopsy on January 22 and 24 showed no change. At necropsy sections of the vulva showed marked necrosis and infection. The cell protoplasm was granular and hyperchromatic, and the nuclei were large. Superficial necrosis and infection were widespread.

CASE 3.—E. M., white, married, aged 44 years, was admitted on Jan. 2, 1940. She appeared to be in good condition, and was obese and comfortable. She had received 3,800 mc.hr. of radon eight weeks before admission. Biopsy of cervix showed columns of large and small epithelial cells, scant stroma, and pearl formation.

An attempt was made to conduct roentgen therapy and local refrigeration simultaneously, removing the applicator during x-ray treatment. Refrigeration was begun on January 20 and discontinued four days later because of moderate vaginal bleeding. Repeated hemorrhages then occurred and five transfusions were neces-

sary. Roentgen therapy was discontinued. On March 26 she had improved so much, that refrigeration was resumed. After twelve hours, with local temperature at 60° F. oral temperature fell to 94° F., and she became very drowsy. She died in coma five days later, blood urea rising to 64 mg. per cent.

At necropsy the posterior fornix was found completely necrotic with a rectovaginal and a vesicovaginal fistula; the ureters were patent, but narrowed. Sections of the pelvic tumor showed sheets and columns of large epithelial cells supported by a very scant amount of connective tissue, and surrounded by broad zones of necrosis, the nuclei were large, and the cytoplasm granular. Sheets of tumor cells were present in the body of the uterus.

CASE 4.—F. F., white, single, aged 40 years, was admitted on Feb. 17, 1940. She had received full irradiation seven months before. Biopsy had shown epidermoid carcinoma of the cervix, Grade II. Her urine showed numerous pus cells, and the blood urea was 46 mg. per cent. Vaginal examination showed a large crater about one inch from the introitus, involving the entire cervix and vaginal vault. The pelvis was filled bilaterally and posteriorly by a dense nontender mass. Urography showed moderate right hydronephrosis; function of the left kidney was nearly absent.

Refrigeration was begun on Feb. 24, 1940, and discontinued on March 2, because of marked edema of the labia and sloughing areas in the lower third of the vagina. An average temperature of 48° F. was maintained during this time. On April 15 refrigeration was resumed, and continued until April 22, with vaginal temperature maintained between 40° F. and 50° F. During the second trial of therapy, she became drowsy and confused, and died in coma nine days later. Blood urea at that time was 71 mg. per cent.

Biopsy on March 9 showed a broad zone of squamous epithelium covered with a thin layer of keratin. In other areas the dense anaplastic squamous cells showed indistinct cell outlines, scant cytoplasm, and nuclei which varied in size and staining characteristics. The stroma was hemorrhagic, and contained many round cells and plasma cells.

At necropsy the entire vaginal vault was necrotic, with a rectovaginal fistula. The left ureter was destroyed just proximal to the bladder, with its separated ends entering directly into the pelvic crater. Section of the tumor tissue showed irregular cords of epithelioid cells invading the cervix and uterine corpus. In many cells the nuclei were hyperchromatic, in others the nuclei were pale and vacuolated.

CASE 5.—J. M., white, married, aged 48 years, was admitted on Jan. 10, 1940. Irradiation was incomplete. On vaginal examination there was a large stony-hard irregular mass about the cervix, with a deep central crater. Urography showed complete closure of the right ureter, and stenosis of the left ureter with hydronephrosis. On biopsy of the cervix extensive epidermoid carcinoma Grades I and II was found with cells varying in size, shape, and staining quality, containing moderate cytoplasm and large hyperchromatic nuclei; evidence of severe infection was present.

Refrigeration was begun on January 12 and continued between 50° F. and 55° F. until January 16 when the patient became euphoric and disoriented. On February 24 a severe acute suppurative parotitis was incised and drained with recovery of a hemolytic *Streptococcus aureus*. Her condition became steadily worse, with death in coma on March 12. Blood urea rose progressively, finally reaching 320 mg. per cent. The size of the pelvic mass remained unchanged.

The last biopsy on Jan. 25, 1940, showed epithelioid cells with scant cytoplasm and very large nuclei; cell outlines were indistinct and vascularity pronounced.

CASE 6.—M. G., colored, married, aged 31 years, was admitted on June 22, 1940. The pelvis had been fully irradiated four months before. Pelvic examination showed a large crater in the vaginal vault, surrounded by nodular cartilaginous-like parametrium. The right kidney was hydronephrotic. Biopsy showed an epithelioid cervical carcinoma of high malignancy with evidence of infection.

Refrigeration was begun on July 5 and continued at 55° F. until July 15 when the patient became very drowsy. On July 17 she died in a convulsion, with blood urea steadily rising to 67 mg. per cent.

Biopsies showed no degenerative changes. On July 9, cell outlines in the cords of malignant cells were indistinct, the nuclei varying in size, shape, and staining intensity. Later biopsy showed nothing of interest.

COMMENT

In May, 1940, Lawrence W. Smith[3] emphasized the experimental nature of the Temple University studies and stated that no patients had ever been accepted for treatment with expectation of a favorable outcome, but only for relief of pain and clinical study of the effect of low temperatures upon the life of cancer cells. Both Fay and Smith have warmly recommended the use of low temperatures as an adjunct to present methods of treatment, since they have continued to observe important cell changes in cancer. They found that whenever it had been possible to apply apparatus to the lesion so that the approximate delivered temperature would lie between 40° and 50° F., no case was observed in which striking regression of the tumor mass did not occur. Pain was consistently relieved in their cases.

Our cases are too few in number to warrant definite conclusions. It is well known that local cold will cause death of tissue, if the temperature is low enough and maintained. That there is a critical temperature which will bring about destruction of cancer cells without harm to normal cells is possible. It is clear that effectiveness of local refrigeration therapy must depend upon discovery of this optimal temperature, complete coverage of the lesion and satisfactory maintenance of temperature control in the entire depth of the diseased area. Construction of mechanical apparatus intended to cover the deep and wide parametrial outgrowth of carcinoma of the cervix is difficult and the penetration depth of the delivered temperature is unknown.

The implications of proximity of the bladder, rectum, and ureter must be seriously considered. The effect of previous irradiation on the pelvic tissues further complicates the problem. Occlusion of one or both ureters with consequent impairment of renal function is commonly associated with carcinoma of the cervix. There is no evidence, of course, that destruction of the ureter in two of our cases was due to refrigeration, yet it is an infrequent finding. Ewing[4] says: "The natural termination of most cases of uterine cancer is through uremia from occlusion of the ureters. . . . These important structures are commonly invaded from without through the parametrium, and while the wall long resists destruction, partial or complete occlusion is readily established by inflammatory processes. The ureter may also be invaded by extension through the bladder wall, and it may be occluded by inflammation extending upward from the bladder. Dilatation of the ureter, hydronephrosis, and chronic nephritis with gradual suppression of the renal function regularly follow."

Regression in size of the tumor mass seems encouraging, but in cancer of the cervix, it is relatively unimportant. Pain may be relieved by other methods with much less danger.

SUMMARY

Ten patients with advanced genital cancer, 9 cases of carcinoma of the cervix, and 1 case of carcinoma of the vulva received local refrigera-

tion therapy. In 6 cases the duration of therapy was 96 to 900 hours. Temperature was maintained between 40° F. and 50° F. in 1 case, at 50° F. in 3 cases, at 50° F. to 55° F. in 2 cases, and 60° F. in 1 case. Control of temperature was satisfactory.

Notable diminution in size of the tumor mass was observed in 3 cases, and pain was relieved in 2 cases.

Serial biopsies showed cellular degenerative changes in only 1 case. Marked necrosis of the cancerous refrigerated area was found at necropsy in 3 cases, in 2 of which fistulas were present with complete destruction of the ureter. Death occurred in coma in 4 cases, and it is our opinion that death was hastened by local refrigeration therapy.

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182 CLINTON STREET

III. MEDICAL STATUS AND PSYCHOLOGIC ATTITUDE OF PATIENTS FOLLOWING ABORTION*

A FOLLOW-UP STUDY OF 100 CASES

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MUCH is said of the aftereffects of abortion, but little is known. It has been shown that active treatment of incomplete abortion shortens the time of hospitalization and permits the patients to resume their usual occupations earlier than does palliative therapy. Many advocates of the latter method of treatment maintain, however, that curettage is more likely to be followed by abnormalities of menstruation, chronic invalidism, and sterility. This view is always brought forward in discussion after any paper which presents a series of cases actively treated. That *immediate* morbidity and mortality are not increased by operation has been repeatedly demonstrated. We have been unable, however, to find any report in the American or English literature which throws any light on the *remote* results of curettage for incomplete abortion.

This is a report of a follow-up study of 100 patients seen at the Bellevue Hospital Gynecological Clinic a short time after hospitalization for illness associated with the early interruption of pregnancy. These women had all been interviewed previously by me, having been included in the series of 537 cases reported earlier.[1] On discharge from the ward all 537 were instructed to return to the Clinic for check-up in four

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weeks. The present group consists of those who obeyed instructions to the extent of coming back on the day on which the postoperative clinic is held. It is unavoidably selective, being probably overweighted by those who did not feel that they had made a proper return to health. These would, no doubt be more inclined to seek the clinic than those who felt well and who, therefore, would be less likely to take the time for a procedure which would seem to them unnecessary. For this reason the proportion of morbidity shown here is probably considerably higher than would be found could the entire original series be interviewed and examined.

Patients were interviewed by the author and examined by the resident and visiting staff of the Bellevue Gynecological Service detailed to the postoperative clinic. Twenty-two of the 100 patients had admitted illegal induction; 8 had had therapeutic abortions; 70 had denied voluntary interference.

The great majority (89) of these patients were seen from three to six weeks after leaving the hospital. The account they gave of their behavior and emotions had altered considerably in this time.

Two of those who had previously admitted attempts to rid themselves of the fetus by taking supposedly abortifacient drugs, denied such attempt when seen at the clinic. Conversely, two who had denied induction subsequently admitted it. We were surprised not to find more changes in the history relating to induction.

TABLE I. CHANGES IN ATTITUDE TOWARD ABORTION

ATTITUDE AT HOSPITAL INTERVIEW	TOTAL	ATTITUDE AT FOLLOW-UP INTERVIEW				
		REMORSE	REGRET	RELIEF	SATISFACTION	INDIFFERENCE
Remorse	1	--	--	1	-	--
Regret	53	--	32	6	5	10
Relief	16	--	5	6	2	3
Satisfaction	9	--	2	1	6	--
Indifference	12	--	5	3	2	2
No record	9	--	2	4	2	1
Total	100	--	46	21	17	16

Much greater changes occurred in these patients' expression of their subjective attitude toward the abortion, toward their sexual partners and toward coitus. Table I shows that, while a few who had at first been pleased with the untimely termination of pregnancy afterward came to regret it, the general trend with time was toward relief and satisfaction. This may be due to the human tendency to accept *le fait accompli.* One-third of those who expressed satisfaction, relief, or indifference, at the same time complained of mental depression, a feeling of general "blueness," which dated from their recent illness. The attitude toward the sexual partner changed in a manner contrary to what one might expect. Of the 70, who at the time of the abortion expressed love for the partner, 15 had changed to mixed emotion or dislike by the time of the follow-up interview. In 13 cases the sex relationship which had been responsible for the pregnancy had been terminated with feelings of dislike and repugnance on the part of the woman.

The attitude toward coitus had changed even more markedly in the same direction. Of 68 women who had stated in the hospital that they found pleasure in the act, 22 expressed indifference and 10 dislike after return to the home environment. Fifty-seven had resumed coitus when interviewed; 43 had not. Only 57 had refrained until one month or more postabortum.

As stated in an earlier report every effort was made to impress these patients with the importance of postponing pregnancy for a time, and directions were given for reaching the birth control clinics nearest their homes. That this effort had little influence is shown by the fact that of the 57 who had resumed coitus only 60 per cent were taking any precautions to prevent pregnancy. None had visited a clinic. One was referred to the Prenatal Clinic, three months pregnant, four months after a self-induced abortion. The majority of these women eagerly reiterated their wish to be referred for birth control and were again painstakingly directed to convenient clinics.

The management of the original 537 patients has been outlined in the earlier report. Of the 100 who figure in this follow-up study, 95 had been curetted, and 5 had undergone therapeutic hysterotomy and Pomeroy sterilization.

TABLE II. SYMPTOMS (PRESENCE BEFORE ABORTION DENIED)

Total cases	100
No complaint	23
Weakness	52
Tiredness	51
Abdominal pain	33
Leucorrhea	32
Depression	30
Backache	30
Constipation	22
Abnormal bleeding	19
Urinary dysfunction	15
Headache	8
Nervousness	2
Fainting	2

TABLE III. PELVIC PATHOLOGY

Total cases	100
No gynecologic pathology	38
Retroversion uteri	23
Uterus enlarged	9
Uterus soft	3
Cervical erosion	11
Endocervicitis	9
Adnexal or parametrial thickening	2
Adnexal or parametrial tenderness	7
Adnexal mass	5
Cystic ovaries	5
No record of pelvic examination	9

Tables II and III show the incidence of complaints and of pathology found at pelvic examination. While only 38 were pronounced entirely "negative," in most instances the abnormality found was of minor degree. Nearly all the erosions, for example, were described as "slight."

Retroversion is discovered in about 20 per cent of nulligravidas examined routinely without reference to uterine symptoms. In a series of 372 routine pelvic examinations on a group, roughly comparable to the present series in age and parity, but differing in that it was selected for the denial of ever having undergone any type of abortion, the proportion which showed no demonstrable deviation from pelvic normality was 32 per cent, or slightly less than found here. In the same study, a group of 128 who gave a history of spontaneous or induced abortion presented only 25 per cent who could be said to have perfectly normal pelvic organs. The treatment the latter group received at the time of abortion is not known. A follow-up study on a series of patients treated palliatively would be of great value for comparison.

The author wishes to express her indebtedness to Dr. William E. Studdiford for his cooperation and encouragement without which this study would have been impossible.

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OBSERVATIONS ON THE POSSIBLE RELATIONSHIP OF DIET TO THE LATE TOXEMIA OF PREGNANCY

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IN RECENT years the idea has been advanced that diet and nutrition may bear a definite relationship to the development of the late toxemias of pregnancy. Ross[1] found that in North Carolina the prime factor in maternal mortality was toxemia and that the number of cases of toxemia among ill-nourished obstetric patients was out of all proportion to that found among their more fortunate sisters.

In our southeastern states, deaths from eclampsia[2] are more frequent in proportion to live births than are such deaths in our more prosperous northern states. It has accordingly been assumed that some factors in this area predispose to a development of a disproportionate number of cases of toxemias during the latter months of pregnancy. The number of toxemias admitted to certain obstetric hospital services in the south is high, but it is difficult to get accurate figures from their prenatal clinics showing the percentage of toxemias to pregnancies of entire populations. The many deaths due to eclampsia do not necessarily result from an increased rate in the development of toxemia, but to inadequate prenatal care. If one can show that far more toxemias of pregnancy develop in one area than in another, a comparison of eating habits, mode of life, etc., may well shed some light on their origin. If, for example, one could find in neighboring communities persons living under generally similar conditions, differing only in one or two particulars, but with a strikingly different incidence of pregnancy toxemias, an investigation of their variances might well be illuminating. To us it seems that valuable information may result if studies can be made for comparison of rates of

toxemia and living habits of different population groups, in areas of states that have a high incidence of eclamptic deaths.

The present study concerns itself with a rural, almost wholly white population in the hills of southeastern Kentucky, cared for entirely by the Frontier Nursing Service. A population of between 8,000 and 9,000 people, living in a relatively inaccessible territory of 700 square miles, is cared for by a physician (the author) and about 20 well-qualified nurse-midwives. There is no physician other than the Medical Director of the Service in the entire area. The Service maintains one hospital of 20 beds. From Sept. 3, 1925, until Jan. 11, 1940, we have cared for 4,004 regular registered obstetric cases, with a maternal mortality of 1.25* per 1,000 deliveries. It is on these cases that this study has been made. In normal cases, prenatal examinations have been made monthly from the date of registration for the first six months of pregnancy, bi-monthly for the next two months, and weekly for the last month of pregnancy. The delivery is usually conducted by the nurse-midwife in the home. Post-partum calls are made (depending on the distance from the nursing center) daily or every other day for the first ten days, and then weekly until the end of the month.

TABLE I. INCIDENCE OF TOXEMIA*

	MILD	SEVERE	ECLAMPTIC	TOTAL
Primigravida	9	12	7	28
Multigravida	67	24	3	94
Total	76	36	10	122
Percentage incidence	1.9%	0.9%	0.2%	3.0%

*In addition we have a smaller group of cases, 438, which have been excluded. These are emergency cases in which the patients have not received full obstetric care. In this group there were 24 patients with toxemia; mild 13, severe 6, and eclampsia 5. The incidence of toxemia for the combined groups is 3.3 per cent.

In the entire group of 4,004 patients, there were 122 patients with toxemia of pregnancy. These are shown in Table I. This classification based on the clinical evaluation of the patient in terms of blood pressure changes and the presence or absence of albuminuria, edema, and toxic symptoms. (Laboratory facilities for special diagnostic procedures were not available.) A systolic blood pressure of 140 was used as the starting point of toxic hypertension. Since most of the blood pressures were taken with a Tycos instrument, and by palpation, the records do not show the diastolic blood pressure. The observation of nephritic changes was limited to the presence or absence of albuminuria, as determined by the heat acid test. Needless to say, there are a number of possible combinations of these criteria.

The beginning and the termination of the toxic period was based on hypertension and albuminuria as reported on the records of the respective patients during the prenatal period. Puerperal blood pressures and urinary findings are not included, since they were not recorded for the entire group. Such findings were considered toxic if found on two or more consecutive prenatal visits. However, there were 6 patients

*Gross maternal mortality rate.

who did not have toxic albuminuria or hypertension on consecutive prenatal visits, but who did have symptoms sufficiently marked to warrant their inclusion: 3 in the mild group, 1 severe, and 2 with eclampsia. The average number of prenatal visits for these three groups during the toxic period was as follows: mild, 5.5, severe, 12, and eclamptic, 2.2.

In terms of blood pressure changes, there were 80 patients in whom the blood pressure ascended from 30 to 50 points to reach the given toxic level of 140. There were 28 patients with blood pressures above this point when first seen. There were 14 obviously toxic patients with blood pressures below this point during their entire toxic period. There were 13 patients in the hypertensive group whose pressures dropped below 140 prior to delivery, only 2 of these were not toxic at the time of delivery.

There were 76 patients with albuminuria, 28 with plus one albuminuria, 48 with plus two to plus four albuminuria.* In addition to those with toxic hypertension and with albuminuria, there was one patient with a toxic psychosis, which was due to pyelitis of pregnancy. This is the only instance in which a toxic state was secondary to pyelitis of pregnancy. There were 82 patients with associated edema, while 93 manifested toxic symptoms.

Among those with hypertension and albuminuria are included 20 patients whose toxic state was superimposed on a definite chronic nephritis or chronic hypertension, 8 and 12, respectively. This incidence probably does not include all such cases, as there is a lack of adequate information on the group in the nonpregnant state. There were 7 patients in whom the toxic state was repeated one or more times. These individuals accounted for 11 cases of toxemia.

Of the 10 cases of eclampsia, 8 appeared in the intrapartum period, two in the post-partum period. All were of an acute fulminating nature with a toxic period of from two days' to two weeks' duration (9 patients one week or less, 1 patient two weeks' duration). Seven of these patients had prenatal care of from three to twenty weeks prior to the toxic period, while 3 were toxic when registered.

The various time factors of the toxemia group were tabulated to show the duration of the gestation at the time of registration, the duration of the toxic period, and the calendar months involved. One-half of the patients registered from the tenth to the twenty-sixth week of their pregnancy. The other half registered after the twenty-sixth week. The average duration of the gestation at the time of registration for the entire group was 26.3 weeks, and for the toxic group, 25.7 weeks (mild, 25.7 weeks; severe, 24.9 weeks; and eclamptic, 30.4 weeks). The duration of the toxic period ranged from 21 weeks to less than 1 week, with the average for the entire group 4.9 weeks, and for the particular classifications: mild, 5.5 weeks; severe, 4.7; eclamptic, less than 1 week. In all but 8 patients the toxic period persisted until the termination of the delivery.

To show the seasonal incidence of this toxic group, the calendar year was divided into four equal periods: winter (December-February), spring (March-May), summer (June-August), and fall (September-November). When the toxic periods were arranged according to their

TABLE II. SEASONAL INCIDENCE OF TOXEMIA (PATIENTS WITH TOXEMIA)

	WINTER	SPRING	SUMMER	FALL
Mild	21	38	11	6
Severe	6	12	16	2
Eclamptic	6	2	2	0
Total	33	52	29	8

*Test done routinely on freshly voided specimen. Plus one albuminuria up to the point where the solution becomes opaque.

corresponding calendar weeks, it was found that 70 per cent of the cases appeared in the winter-spring season and 30 per cent appeared in the summer-fall season. Table II shows the incidence of the toxic cases in the four seasonal divisions. Dividing the total deliveries according to the seasonal distribution, we find: winter-spring, 2181; summer-fall, 1823; showing 54.5 per cent in the winter-spring period, and 45.5 per cent in the summer-fall period. It is evident that the seasonal variation in the incidence of toxemia cannot be accounted for by the variation in the total number of registered obstetric patients alone.

Table III shows the mortality incidence of the toxic group.

TABLE III. MORTALITY

	MILD	SEVERE	ECLAMPTIC	TOTAL
Total births	82	39	11	132
Full term stillbirths	2	1	2	5
Premature stillbirths	2	4	1	7
Neonatal deaths	0	1	0	1
Maternal deaths	0	1	0	1

There was a total of 132 births including 1 set of triplets, and 8 sets of twins. There was one anencephalic monster, and one macerated fetus. There were two non-viable fetuses of twenty-four weeks' gestation delivered of mothers with severe toxemia. There was one neonatal death, a premature infant who lived five days. There was one maternal death, that of a patient with severe toxemia who died on the seventeenth day of the puerperium from cardiorenal disease.

The foregoing obstetric analysis is of additional interest in view of the low income of the respective families. In this area the total income per family, including the cash value of crops, milk, meat from the cattle and the pigs, is $364.00 per year.[3, 4] As a direct result, the diet on which most of the people live is considerably less than that usually considered a minimal one for health.[5] This was substantiated by a nutritional survey[6] which was conducted in 1939 (February, March, April, May). Chart 1 shows the dietary of these families in the winter-spring period, as obtained from 330 families, 24 per cent of the total families carried by the Frontier Nursing Service, and indicates the frequency with which they consume available foods. Most of the foods consumed are produced locally. With poor soil for farming and with very low cash income, the diet is necessarily limited. However, it does afford a basic fare compatible with active life, and does protect against the usual deficiency diseases.

In addition, it was our good fortune to have a study made of the nutritive value of the diets of some of our obstetric patients. For this purpose, we had the services of an experienced nutritionist who personally conducted the survey. The survey was done in the fall period (September, 1939). The results are given in Table IV. Seventeen of the patients were in the last trimester of the prenatal period, while 3 were in the post-partum period. The entire group were normal obstetric patients.*

It is evident that this group of patients are living on minimal dietary requirements as compared with diets which have been generally considered as optimal for obstetric patients.[7] A number of the patients are

*Patient 15 in the chart had had pellagra in the early part of her prenatal period, and was successfully treated with nicotinic acid.

way below the adequate caloric intake, and many are on the borderline or below the usual vitamin requirements. The protein values are especially low, but most of the patients receive 10 per cent or more of their total calories from this type food. The diet is low in carbohydrate, but they do receive a generous supply of fat. The low vitamin intake, however, does afford protection against deficiency diseases. During the period of the author with the Service (nine years), there have been 3 obstetric patients with deficiency diseases (2 patients with pellagra, and a third with neuritis). It is significant that this dietary was obtained in the season of the year (early fall) when the supply of food available for consumption is more plentiful. It is also the season in which we found our lowest rate of toxemia. On the other hand, the greatest number of our toxic cases appeared in the winter-spring period, which is also the period in which the food supply is most restricted.

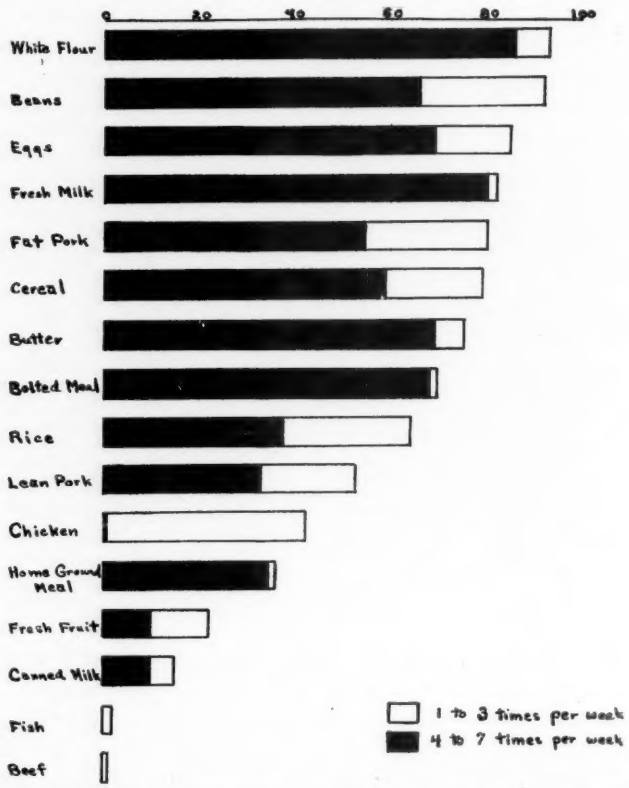

Chart 1.—Food habits of the rural group. Comparison of consumption of food items 1 to 3 days per week and 4 to 7 days per week by percentage of total families.

The toxemia rate reported shows a total incidence of late toxemia of pregnancy of 3 per cent, from a rural group of patients who have received adequate prenatal care. In this group only 10 patients (0.2 per cent) developed eclampsia. There were no maternal deaths due primarily to toxemia. (The one reported death occurred in the third week of the post-partum period from cardiorenal disease.) These

TABLE IV. THE NUTRITIVE VALUE OF THE DIETS OF TWENTY PREGNANT WOMEN

CASE	GM. P.	GM. F.	GM. C.	TOTAL CALORIES	MINERALS			VITAMINS INTERNATIONAL UNITS			SHERMAN BORQUIN UNITS
					GM. Ca.	GM. P.	GM. Fe.	A	B_1	C	G (RIBOFLAVIN)
1	31	72	200	1,572	0.573	0.649	0.0048	1,371- 8,277	98	882-1,218	185-306
2	49	66	320	2,070	0.812	1.152	0.0094	2,778- 4,089	200	749-1,504	353-482
3	62	150	354	3,014	1.392	1.343	0.0137	3,006-28,109	263	937-1,881	711-786
4	73	106	436	2,990	1.465	1.830	0.0145	4,217-23,228	321	1,564-3,203	547-852
5	56	125	294	2,525	0.431	1.146	0.0696	2,232- 4,288	240	386- 738	149-149
6	44	54	385	2,202	0.232	0.995	0.0421	1,627- 3,469	194	1,052-1,588	147-220
7	39	95	354	2,427	0.248	0.571	0.0111	1,652-12,065	163	594-1,153	153-188
8	82	156	398	3,324	1.441	1.723	0.0254	2,421- 2,777	237	777-1,516	431-701
9	44	68	265	1,848	0.751	1.043	0.0065	1,686-10,716	194	772-1,369	270-413
10	70	95	258	2,167	0.234	1.648	0.0098	2,430- 5,428	238	283- 414	55- 75
11	37	69	167	1,437	0.530	0.811	0.0152	965- 2,340	189	433- 913	117-190
12	61	128	315	2,656	1.491	1.338	0.0126	3,029- 9,344	291	1,682-2,785	513-850
13	74	105	272	2,329	1.591	1.869	0.0138	2,681- 5,733	293	1,346-1,950	578-886
14	42	51	282	1,755	0.145	0.926	0.0099	477- 663	174	238- 370	62- 91
15**	39	81	261	2,019	0.595	0.703	0.0168	2,738- 5,716	117	485-1,056	163-276
16	64	88	394	2,642	0.715	0.977	0.0114	3,950- 7,999	244	783-1,364	186-266
17	41	106	247	2,106	0.383	0.761	0.0101	1,637- 3,950	184	448-1,062	107-145
18	45	56	214	1,540	0.262	0.774	0.0099	1,421- 4,891	162	358- 486	73- 96
19	45	69	217	1,669	0.415	0.736	0.0071	1,127- 2,991	139	383- 871	223-377
20	34	69	292	1,925	0.413	0.754	0.0080	1,781-19,802	209	648-1,089	224-305
Medians for the 20 patients	45	84.5	287	2,136.5	0.5515	0.986	0.01125	1,733- 5,572 4,168	197	698.5-1,185.5 698.5	185.5-290.5 235.75

Median age, 29 years; median weight, 137½ pounds

**The birth weights are available on 130 of the total deliveries. The range in the combined live and stillbirth weights is as follows: minimum, 1 12/16 pounds; average, 7 5/16 pounds; maximum, 12 pounds.

findings appear to be low as compared with other available reports.[8-10] Such reports, however, are from private practices, or from city clinics, and are not fully comparable since they represent urban or semi-urban individuals and do not indicate the toxic rate for an entire group (or population area). With surveys which were comparable, one could determine whether or not there were significant sectional differences in the amount of toxemia, and whether or not habits and modes of life were contributing factors.

CONCLUSIONS

1. The incidence of toxemia is reported from a rural group who have received complete obstetric care from the staff of the Frontier Nursing Service.
2. The incidence is reported in terms of the general types of toxemia and according to the season of the year in which they occur.
3. The diet studies of normal obstetric patients in this area are given. This indicates a low protein, low carbohydrate, high fat diet.
4. There does not seem to be any causative relationship between the incidence of toxemia reported and the current diet.
5. There appears to be a direct relation between the seasonal incidence of toxemia and the seasonal scarcity of food.

I wish to express my appreciation for the helpful advice given by Dr. Robert Lewis of Yale University, New Haven, Conn., and by Dr. M. Blankenhorn of the University of Cincinnati, Cincinnati, Ohio. I am indebted to Miss Jean Grant of the Medical Department of the University of Cincinnati, Cincinnati, Ohio, for the "Nutritive Diet" chart. Valuable assistance was rendered by Miss D. Buck, Assistant Director, and by Miss G. Weeks, Statistician, of the Frontier Nursing Service, Wendover, Ky.

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IRRADIATION OF BENIGN PELVIC LESIONS

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THE earliest record of an attempt to control uterine bleeding by irradiation in the University of Michigan Hospital was in 1904, only a few years after the discovery of x-rays. Since that time improvements in equipment and technique have been made which enable one to be fairly accurate in applying various doses of radiation. The use of radiation for this purpose, however, has not been generally accepted on the grounds that the menopausal symptoms produced were more severe than those associated with spontaneous menopause or surgical castration. Notwithstanding recent reports in the literature to the contrary, the opinion seems fairly widespread that the psychic changes observed after irradiation are much more pronounced than after the normal menopause, and that a frank psychosis or severe impairment of health may result.

The objectives of this study were: (1) to determine the efficiency of irradiation in the control of uterine bleeding, (2) to evaluate the menopausal symptoms which might ensue, and (3) to improve our method of applying roentgen radiation for the purpose of castration. A report by Kretzschmar and Gardiner of this Clinic concerning surgical menopause in hysterectomized patients will be used as a basis for comparison in evaluating menopausal symptoms.

This report is based on the records of 334 patients treated with x-ray or radium for benign pelvic lesions. These patients received their treatment during the period July 1, 1925, to July 1, 1937, and the follow-up information was obtained by questionnaire or examination six or more months after treatment. Most of the patients were 40 years of age or older, only 45 of the 334 being in the younger group. The complaint on admittance in 260 (78 per cent) of the 334 patients was abnormal uterine bleeding. This included excessive or irregular bleeding at the menopause in patients without palpable changes, bleeding from uterine fibrosis or small fibromyomas and, in a few instances, excessive bleeding in young adults without demonstrable pelvic abnormalities which had failed to respond to conservative measures. All of these patients were curetted on one or more occasions, and material so obtained was examined carefully microscopically to rule out the presence of malignancy. A smaller group, 52 in number (15 per cent), had chronic pelvic inflammatory disease. Most of these patients had as one of their symptoms some abnormality of menstruation or had exacerbations of pelvic symptoms at the time of the period. The majority were individuals beyond forty years of age in whom surgery was not thought to be indicated. Endometriosis was present in 9 patients (3 per cent).

In the remaining 13 per cent, castration was planned because of debilitating extrapelvic lesions, such as carcinoma of the breast and advanced pulmonary tuberculosis.

The technique of administration and the dose of radiation required to produce castration* varies considerably in the reports of different authors.[2, 3, 5-10] These reports also suggest that it is not common practice to vary the roentgen dose according to the size of the patient.

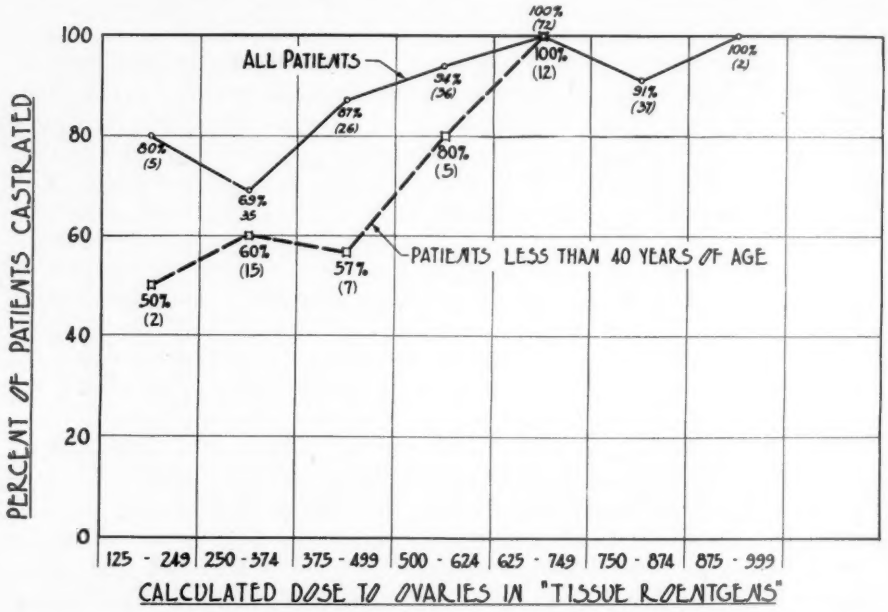


Fig. 1.—The efficiency of different roentgen ray doses delivered to the ovaries in producing permanent castration.

This fixed dosage was also used for many of the patients in this study early in the period covered by this report. In later years, this procedure was altered according to the patient's weight, and sufficient information was available in the records of 213 patients to calculate the roentgen dose to the ovaries. The depth dose and backscatter figures for water phantoms by Arenson and Quimby[11] and the isodose curves of Weatherwax[12] were used in this calculation. These cases were grouped according to computed ovarian dose and efficiency of castration as shown in Fig. 1. Any recurrence of uterine bleeding two or more months following irradiation and lasting more than one day was considered a failure of castration. This definition was adopted to exclude "spotting."

It should be noted that 5 of the 6 patients receiving the smallest amount of irradiation given in this series (125 r. to 249 r.) and intended as a temporary or subcastration dose were castrated permanently. As the dose of radiation increased, the percentage of patients castrated similarly increased. Since younger individuals (under 40

*The word castration is used for want of a better term to imply cessation of ovarian function responsible for menstruation rather than removal of the ovaries.

years of age) were castrated in a smaller percentage of instances with similar doses, it appears that at least 625 r. to 749 r. to the ovary is necessary in order to assure permanent castration regardless of age (Fig. 1). Castration doses reported in the literature[1, 5, 10, 16] have not indicated that such large amounts are necessary.

Some of the patients in this series received 600 to 1,000 roentgens (surface dose measured in air without backscatter) to each of two pelvic ports delivered within a few days. In a number of instances this caused temporary bladder, bowel, and skin irritation. In order to overcome this difficulty, a new technique of irradiation was devised. This method employs large anterior and posterior ports which are divided along the midline of the body by a 2 cm. strip of lead rubber, making in effect two anterior and two posterior ports centered approximately over the ovaries. By using in addition, two lateral ports, the necessary anterior and posterior skin dose can be reduced by approx-

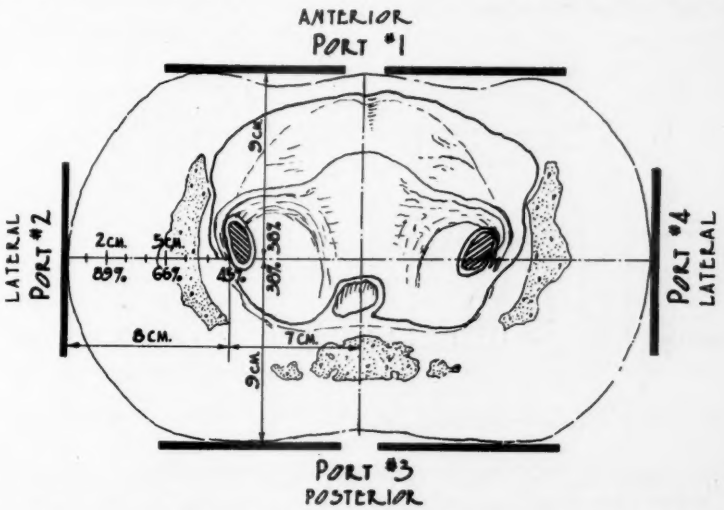


Fig. 2.—Method of calculating total depth dose in "tissue roentgens" delivered to each ovary. Cross section of female pelvis at level of symphysis pubis.

imately one-third (Fig. 2). Fig. 3 shows the size and location of the ports and the surface dose of radiation (measured in air without backscatter) which must be applied to each of the six ports to deliver 625 roentgens to the ovaries of patients with various pelvic measurements. Since using this method of application, a definite decrease in discomfort has been noted.

There were 58 patients treated by irradiation whose pelvic measurements were not recorded. These were not included in the previous charts but are included in the study of clinical symptoms.

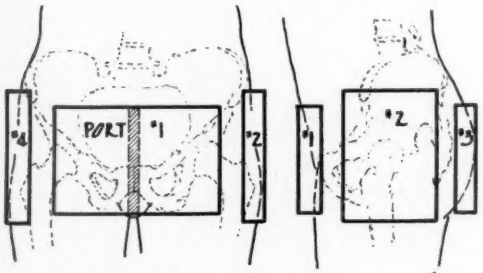
Sixty-three patients were treated by means of an intrauterine application of radium. As shown in Fig. 4, 1,000 to 1,500 mg. hr. of radium (1.5 mm. platinum filter) were efficient in 77 per cent of the cases. While the group receiving more than this amount is too small to permit conclusions, it is probable that 1,500 to 2,000 mg. hr. should be sufficient

for castration in most instances. Attention is called to the one patient who received less than 500 mg. hr. and yet was permanently castrated. Here, as with x-ray in small doses given for temporary or partial castration effect, sufficient uncertainty exists to offer a serious objection to their use in young individuals with the hope that symptoms will be controlled without interference with fertility in later years.

There were no deaths following either x-ray or radium in this series. Two patients had a febrile reaction after treatment, one patient receiving x-ray and another radium. The cause of the fever was not apparent from clinical investigation but was assumed to be a mild exacerbation of a quiescent inflammatory process in the pelvis. Neither of these patients was acutely ill but represented a postirradiation febrile morbidity of 0.6 per cent.

FACTORS:

200 K.V. (MAX), 0.50 MM. CU. + 2.00 MM. AL.
H.V.L. 0.80 MM. CU., T.S.D. 70.00 CM.
ANT. AND POST. PORTS 20×12 CM.
LATERAL PORTS 15×12 CM.



DO NOT EXCEED 250r TO EACH OF 2 PORTS PER DAY.

ANT.-POST. DIAMETER OF PELVIS (SYMPHYSIS)

TRANSVERSE DIAMETER CM.	14	16	18	20	22	24	26
24	285	310	345	375	410	445	
26	300	330	365	400	435	480	525
28	315	345	385	425	465	515	570
30	330	365	405	455	500	560	615
32	345	385	435	480	540	610	675
34	360	405	460	515	580	660	740
36	375	422	480	545	620	710	800
38		440	505	580	660	765	870
40			530	610	695	815	945

Fig. 3.—Permanent castration by roentgen rays. Doses for various sized individuals, using anterior, posterior, and lateral ports. Total dose per port (measured in air without backscatter) required to deliver 625 "tissue roentgens" to the ovaries.

Among the 286 patients followed one or more years after castration, one patient developed carcinoma of the cervix (0.34 per cent) eleven and one-half years after castration by irradiation.

All of the 334 cases were included in evaluating clinical symptoms. They were divided into main groups: the castrated and the noncastrated according to the definition previously given. Each group was studied with regard to the two symptoms usually associated with the menopause; namely, hot flushes and change in sex life. No attempt was made to obtain information concerning the severity of the hot flushes, because as pointed out by Kretzschmar and Gardiner,[15] such data are highly unreliable. Of the 160 patients who were castrated and were free from hot flushes before irradiation, 118 (73 per cent) developed this symptom following treatment. Furthermore, among the 32 patients not castrated, 62 per cent developed hot flushes. In the study of surgical castration, 86 per cent of the patients developed hot

flushes after bilateral oophorectomy and 58 per cent developed them after hysterectomy with ovarian conservation. From this, one may conclude that the incidence of hot flushes after castration by irradiation is somewhat less than following bilateral oophorectomy. Furthermore, these figures (58 per cent and 62 per cent) suggest that subtotal hysterectomy with ovarian conservation will alter ovarian function to almost the same extent as incomplete castration by irradiation.

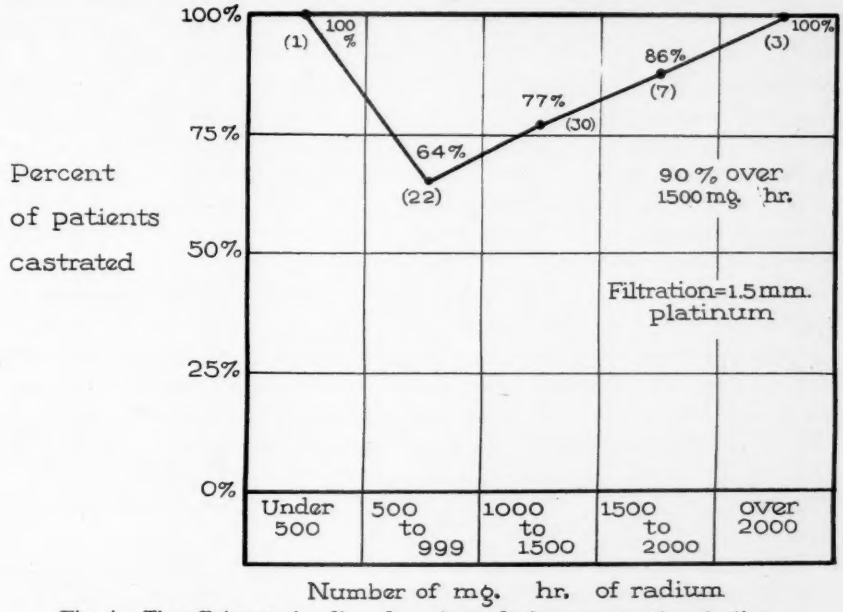


Fig. 4.—The efficiency of radium doses in producing permanent castration.

In many instances, the maintenance of sex life is of far greater importance to the patient than the presence or absence of menopausal symptoms. In order to permit accurate comparison, the wording of our questionnaire regarding libido was similar to that used by Kretzschmar and Gardiner in their study of hysterectomized patients. In the 253 castrated women studied, 108, or 42 per cent, reported a decrease in libido, while 145, or 58 per cent, reported either no change or an increase. In the 63 patients who had a recurrence of menstruation, 23, or 36 per cent, stated that there was a decrease in libido. Comparing this with the effect of surgery, it is noted that the surgical and radiation effects are about the same. Since this group consisted of patients of all ages, an attempt was made to eliminate the factor of advancing years as a cause of decrease in libido by considering only patients under 40 years of age. In this group only 10, or 22 per cent, of the 45 women who were castrated noted a decrease in libido. From these figures it appears that both libido and hot flushes are to a certain extent independent of the ovarian secretions responsible for menstruation.

Although no figures concerning general health are available for comparison, it may be stated that there were no replies suggesting impairment of health, either mental or physical, and that there were many comments indicating a marked improvement.

DISCUSSION

The use of radiation in adequate dosage, either x-ray or radium, appears to be an efficient means of controlling benign bleeding. It is most applicable in women approaching the menopausal age who have completed their reproductive activity. The age at which a patient should be considered as near the menopause is debatable but since reports on large series of cases indicate that the menopause occurs before forty years of age in 5 to 12 per cent of women, and between 40 and 45 in 75 per cent to 80 per cent of the women, a woman of 40 or over may be considered as approaching the menopause. In properly selected cases in this age group, radiation is preferred to hysterectomy because, (1) it has proved to be efficient, (2) it is practically without risk, and (3) it is much more economical. Furthermore repeated observation of these patients gives rise to the impression that the menopausal symptoms which develop are no more severe nor of longer duration than those associated with the normal menopause.

A diagnostic dilatation and curettage should always precede the treatment to avoid overlooking possible malignancy. In the presence of palpable disease of the adnexa, surgical intervention is preferable, since it permits adequate inspection of the pelvic lesion. Furthermore, we are of the opinion when fibromyomas are present which exceed the size of a two and one-half to three months' pregnancy that surgical removal is better than irradiation, because it completely eradicates the lesion, prevents recurrence of symptoms, and avoids complications due to degenerative changes in the tumor.

In young women, radiation should be used only when conservative measures fail or other methods of treatment are contraindicated, since castration by any method is to be avoided in this group whenever possible. Since the methods of temporary or subcastration seem so unreliable, we advise against the use of even small doses of radiation in these patients. If conservative measures fail in the treatment of abnormal bleeding in the young woman, it is felt that hysterectomy is to be preferred, since retention of the ovaries is definitely desirable for their psychic value, and also in the hope that they will retain their endocrine function. Radiation, however, should be used in these patients if they are poor operative risks.

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CLINICAL EVALUATION OF STILBESTROL IN WOMEN WITH HYPOPLASTIC GENITALIA

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THIS report deals primarily with the clinical experimental administration of stilbestrol in patients with hypoplasia of the uterus. The use of this drug was prompted by reports in the literature[1-4] ascribing to it the ability to cause uterine growth, although none of these papers gave satisfactory or conclusive evidence of its value in this respect.

As about 10 per cent of our sterility patients at Bellevue Hospital have definite hypoplastic and underdeveloped uteri one can readily see the value of any therapy that would produce uterine development. We are aware that uterine underdevelopment may be a sign of previous ovarian dysfunction and that it probably indicates concomitant ovarian hypoplasia. Nevertheless permanent uterine enlargement in some of these patients would eliminate at least one causative factor.

In our series 30 patients were given stilbestrol in oil, intramuscularly. With the exception of one menopausal patient all were sterile. There had been only one previous full-term pregnancy and one spontaneous abortion in the entire group.

Of the 30 patients, 28 had unmistakable hypoplastic uteri, among which 5 had secondary amenorrhea, 9 had oligomenorrhea, and 14 had normal menses. Two patients had normal-sized uteri; complaining of oligomenorrhea alone and the other of severe menopausal symptoms. In the entire series, 3 patients had menopausal symptoms.

Dosage.—The dosage of the drug used was 5 mg., three times weekly, except where severe side reactions compelled us to skip an occasional treatment or decrease it to 1 mg., three times weekly. This schedule was followed in all patients except 6. Three patients were started on 1 mg. injections and later increased to 5 mg., while 3 other patients were first given 5 mg. doses, and when they reacted too severely were changed over to 1 mg. injections. Side effects were present in all 6 cases but varied in intensity and number with the dose administered.

This dosage was arbitrarily chosen, some workers having used dosages varying from 1 mg. administered two or three times weekly to 10 and even 30 mg. daily. We were interested in giving a safe but adequate dose to eliminate the possibility of underdosage as a possible cause of failure in development.

Our patients received therapy from a minimum of two injections to a maximum of 42 injections over fourteen weeks. The patient with two injections received one at weekly intervals. She became so extremely sick with nausea, vomiting, and abdominal pain that therapy had to be discontinued. The patient with 42 injections had fifteen years of amenorrhea. She had some early nausea but apparently developed a tolerance to the drug. Her menses did not recur. The average duration of treatment was five weeks. The average number of injections was 15.

Selection of Patients.—In selecting our cases we were guided by our examination of the genitalia, cervix, and uterus, as well as actual measurement of the cervical

canal and of the total depth of the cervix and uterus. All these patients had previously been classified as hypoplastic on admission and measured at the time of tubal insufflation.

Our criterion was not size alone, but the relative proportion of cervix to fundus, the presence or absence of a long supravaginal cervix, the shape and consistency of the fundus, and the shape as well as the size of the cervix.

Patients were rechecked and remeasured before beginning therapy and at frequent intervals thereafter. We measured the length of the cervix to the internal os and then the total length from the external os to the fundus, by means of a graduated sound. In the occasional case where we could find no clear-cut landmark of the internal os, we took only the total length as an indicator. These measurements were made at varying times in the menstrual cycle, and we found no difference in the measurements that could be attributed to the various menstrual phases. We especially did not notice any difference in the internal measurements of the premenstrual uterus versus the postmenstrual. We made no permanent record of any measurements that did not occur on two consecutive occasions. The majority were clinic patients but some were private. With one exception the total length of the cervico-uterine canal was 2½ inches or less.

Symptoms were never inquired into specifically. All side effects and reactions from stilbestrol therapy were offered spontaneously by the patients. From time to time some of the patients were injected with sterile oil without their knowledge and invariably no symptoms were produced on those occasions.

The ages of these patients varied from 22 to 35 years, most of them being between 25 and 30.

They were of average weight, ranging from 120 to 150 pounds. None in the group was excessively thin or excessively overweight.

Result of Therapy.—In not one case did we see any improvement or other effects on the secondary sex characteristics. There was no enlargement of the breasts or labia. Three patients developed engorged, swollen, and painful breasts. Two of these were quite severe, the other only slightly so. One of these patients with oligomenorrhea had had some breast discomfort for many months. Her symptoms were aggravated and persisted for three months after cessation of therapy. In the others, the symptoms cleared up on discontinuing medication.

All breasts were frequently examined, and no patient developed any masses, glands, or other abnormal signs.

Effect on Menses.—Three of the 5 amenorrheic patients showed no effects whatever. One patient developed withdrawal bleeding. She showed a late proliferative endometrium prior to onset of therapy. She received 5 mg. of stilbestrol three times weekly for three weeks, at which time the dosage was reduced to 1 mg. because of the severe side effects, and a second endometrial biopsy taken at this time showed an atrophic endometrium. The fifth patient had had fifteen years of amenorrhea. She developed a profuse gushing, watery discharge per vagina which continued during ten of her fourteen weeks' treatment. She was subsequently curetted under anesthesia, at which time absolutely no endometrial tissue could be obtained even after vigorous efforts.

None of the 10 patients with oligomenorrhea showed any improvement.

Only 4 of the normally menstruating women did not experience some interruption in their menstrual cycle. In 7 of them, the menses were inhibited during administration of the drug and returned shortly after its discontinuance. These patients usually had accompanying nausea and urinary frequency, and as the uteri were enlarged at that time we stopped therapy on all and did Aschheim-Zondek tests on some of them. All of these were reported negative for pregnancy. Two of these patients passed pieces of membranous tissue with the returning menses. We did not do endometrial biopsies on this group during the period of amenorrhea because of the suspected possibility of pregnancy, and we were unable to do them after receipt of the negative reports, as in the meantime they had begun to menstruate shortly after cessation of therapy.

One patient developed menorrhagia and metrorrhagia after the third injection, and this continued until therapy was stopped. Two of the patients developed intermenstrual bleeding.

These menstrual effects clinically resemble those often obtained in cases of cystic and glandular hyperplasia of the endometrium.

TABLE I. EFFECT ON MENSES

	PATIENTS (5) WITH AMENORRHEA	PATIENTS (10) WITH OLIGOMENORRHEA	PATIENTS (14) WITH NORMAL MENSES
No change	3	10	4
Withdrawal bleeding	1	0	0
Menses inhibited	0	0	7
Menorrhagia and metrorrhagia	0	0	1
Intermenstrual bleeding	0	0	2
Serous discharge	1	0	0

Effects on the Uterus.—Of the 28 patients with hypoplastic uteri, only 5 showed either some temporary or permanent change in size or consistency of the uterus. These were all in the group of 7 normally menstruating women whose menstrual cycle was inhibited by the drug. Three of these were temporary and returned to the original condition on discontinuing the drug.

Two of the patients showed permanent changes. The first one showed a permanent increase of 1 inch in the cervical canal, the fundus remaining unchanged on palpation and measurement. This patient was under treatment for eight weeks, during which time she received 120 mg. of stilbestrol which is considered biologically equivalent to 1,500,000 international units of estrone.[5,6]

The other patient received a total of 45 mg. in six weeks. She was so toxic that therapy had to be interrupted for one week. Her uterus increased in size from a total depth of 2½ inches to 3½ inches, the entire increase being confined to the fundus. This enlargement occurred in all diameters as confirmed by palpation.

Side Effects.—The marked discrepancy in the severity and importance of reported side effects is striking, despite the fact that by far the larger number of writers report unfavorable reactions. These differences do not seem to depend on the dosage or method of administration.

For example, while the earlier English writers reported favorable results with a minimum of uncomfortable reactions, Varangot,[7] of France, simultaneously reported very severe gastrointestinal upsets in 8 out of 15 patients.

Very recently Shorr, Robinson and Papanicolaou reported 80 per cent severe reactions in a group of 44 patients, while MacBryde, Freedman and Loeffell,[8] in a preliminary report on 37 patients, stated that in none of their patients was it necessary to withdraw treatment because of toxic manifestations.

In our series, therapy had to be stopped in 60 per cent of the patients because of the severity of the side effects. These consisted of nausa, vomiting, vertigo, headaches, general weakness, and lower abdominal pains in the order of their frequency. In the other cases, therapy was stopped because of interference with the normal menstrual cycle or because of no improvement. These reactions generally occur four to twelve hours after injection and last about twenty-four hours.

Only two patients (or 7 per cent) showed no side effects at all, but both experienced delay in the menstrual cycle. One of the amenorrheic patients began with severe nausea but developed a tolerance, and stilbestrol was discontinued after fourteen weeks because of no improvement. This and the menopausal patient were the only two developing a tolerance to the drug. This tolerance, however, was not complete but relative.

The cause and possible importance of these side effects remain to be determined. Whether they are simply uncomfortable side reactions or indicators of damage to the general body mechanism has not been decided and is still the subject of research. In our series, they certainly were clinically sufficiently severe and uncomfortable as to require extreme ingenuity on our part to convince the patients to continue as long as they did.

Their transitory nature and the fact that our patients showed no residual ill effects for as late as six months would suggest an irritative but nontoxic action. Shorr,

Robinson and Papanicolaou[5] have attempted to throw light on this question by testing its effect on the liver by excretion studies, using both the hippuric acid excretion test and the intravenous bilirubin tolerance test. They compared their results with a series of control patients and also ran simultaneous urea excretion tests. Their results were so variable in both the control and the stilbestrol group that they were unable to draw any conclusion as to its effect on hepatic function.

MacBryde, Freeman and Loeffell, and Buxton and Engle[9] followed a total of 54 patients, and their laboratory studies indicated an absence of any deleterious effect on the liver, kidney, or hematopoietic system in 53 of the patients. It may be interesting to note that MacBryde's series consisted of 12 patients with total ablation of the ovaries and 15 patients with severe spontaneous menopausal symptoms.

TABLE II. SIDE EFFECTS

	NONE	TOLERABLE	INTOLERABLE
Nausea	0	10	18
Vomiting	12	10	8
Anorexia	15	11	4
Headaches	8	8	4
Abdominal pains	11	17	2
Drowsiness and general malaise	22	0	8
Diarrhea	30	0	0
Vertigo	22	8	0

CONCLUSIONS

Except in rare instances this drug does not produce any demonstrable enlargement of the uterine cavity.

It seems definitely to have clinical estrogenic effects.

It produces undesirable side reactions in a large percentage of patients. These may or may not be toxic.

These side effects seem to be at least as frequent and as severe by the intramuscular route as those reported by the oral route.

These side effects are not permanent and disappear with cessation of therapy.

Its effect on the endometrium and on the menstrual cycle seems to resemble closely that of large doses of the natural estrogens.

Tolerance seems to be infrequently developed. There appear to be no cumulative effects from continued use of the drug.

In a small number of patients treated with varying dosages, it was our experience that the side effects varied with the dose administered.

The stilbestrol used in this study was furnished by E. R. Squibb and Sons, through the courtesy of Dr. J. A. Morrell.

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230 EAST FORTY-EIGHTH STREET

THE USE OF EVIPAL SOLUBLE RECTALLY IN OBSTETRICS*

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VARIOUS drugs and combinations of drugs have been resorted to for analgesia and amnesia during labor, since the memorable work of Steinbüchel and Gauss[8] in introducing scopolamine and morphine as the means of alleviating pain during the process of labor. In most clinics in this country, the original "twilight sleep" has been abandoned, because it was found so often to lengthen the process of labor, to cause a high percentage of operative deliveries, and in a large number of cases to produce fetal asphyxia. Morphine seemed to be the most objectionable of the two drug components, also the repeated administration of scopolamine added another undesirable factor. In the search for something better than morphine, various compounds of barbituric acid have been used, either singly or in combination with scopolamine, with more or less success.

At present, the ideal analgesic and amnesic for labor has not been found. There is still controversy in the profession over the ill effects suffered by both the mother and the child from the promiscuous administration of analgesics and hypnotics. This should raise a question as to the value of information given by overzealous individuals in the daily press, magazine articles, and medical commentators on the radio which has often taught the laity to expect or demand too much alleviation from pain during parturition.

Evipal was first used, intravenously, for surgical procedures, requiring twenty to twenty-five minutes for completion. Weber[1] reports that in European clinics over 800,000 patients have received evipal intravenously with but four deaths directly attributable to the drug. This same author also reported on its use intravenously in obstetrics but stated that, because of its short period of anesthesia, it could only be used near the end of the second stage of labor and for that reason it proved to be inadequate.

Gwathmey,[2] in 1936, first reported the use of evipal soluble per rectum, and found it to be a safe and satisfactory means of basal anesthesia. He further stated that the technique was simple and easier to use than ether-in-oil per rectum and that no contraindications to its use were found.

Evipal soluble in obstetrics, by rectal administration, was first reported by Siegler and Beris[3] in 1938. They showed in their 72 cases that this drug was a simple and safe analgesic and amnesic in obstetrics and that there were no deleterious effects on either the mother or the infant.

Evipal soluble is the sodium salt of evipal, known chemically as N methyl-cyclohexenylmethyl barbituric acid. It dissolves readily in water

*The evipal soluble used in this study was furnished through the courtesy of The Winthrop Chemical Company.

and is generally administered in 10 per cent aqueous solution, each 1 c.c. representing 0.1 Gm. of the crystals.

Our series of cases represents 53 unselected obstetric cases at the University Hospital, of which 38 were primiparas and 15 multiparas. All of them received evipal soluble in varying doses by rectal administration, and in conjunction all but 3 patients received scopolamine hydrobromide hypodermically.

ADMINISTRATION AND DOSAGE

The technique of administration of the drug was very simple. Three grams of the crystals were dissolved in 90 c.c. of tap water. To give 1 Gm., 30 c.c. of the solution were used. The patient was instructed to lie on her left side and an ordinary soft rubber catheter was inserted 4 or 5 inches into the rectum. The solution was allowed to run in by the force of gravity or, when necessary, a small "asepto" bulb syringe was used to introduce the solution. The buttocks were pressed together for a few minutes after the catheter was withdrawn and the patient told to retain the solution. The scopolamine was given hypodermically at about the same time as the evipal. An enema should be given some time prior to the instillation of the evipal. All patients in our series received an enema when admitted to the ward and did not receive one prior to the administration of the drug.

The criteria used in determining the proper time for administration of the evipal were, (1) when it was definitely ascertained that the patient was in true labor, (2) when she began to complain of pain and ask for relief, and (3) after the cervix showed effacement and 3 or more cm. dilatation.

In all cases, the initial dose of evipal was 1 Gm. If after one or two hours it was thought necessary, one-half the original dose or the entire original dose was repeated. This was done in only two of our cases.

EFFECT OF THE DRUG UPON THE MOTHER

The effects were found to be quite constant. Generally labor was not prolonged. In this series the average length of labor for the primiparas was fifteen and one-half hours, and for the multiparas twelve and one-half hours. One primipara was in labor sixty-two hours and forty-five minutes, the cause of the dystocia being a rigid cervix which ultimately required Dührssen's incisions and instrumental delivery of a stillborn child. This patient was given evipal soluble, 1 Gm. rectally and $\frac{1}{150}$ gr. of scopolamine hypodermically early in labor and this combination repeated forty hours prior to delivery. It is the only case in which the original dose of evipal soluble and scopolamine was repeated.

Generally, the drug did not stop pains if the patient was actually in labor. However, if it is given too early, i.e., before pains are well established and before effacement and dilatation of the cervix has begun, the patient may go to sleep and labor pains stop entirely. In one of our patients the pains stopped and she went to sleep soon after the drug was administered. The next day labor started again, but this time the drug did not affect the pains and the patient delivered uneventfully following a normal labor.

The time between the administration and actual delivery varied a great deal. The longest time was forty hours and the shortest twenty-nine minutes. In none of these cases were there any ill effects noted

on either the mother or the child. The average length of analgesia was roughly 5½ hours. The length of time required for the onset of analgesia after the administration of the drug averaged about fifteen minutes. At times this was somewhat difficult to determine because the patients were usually awake and responded well although they were often somewhat restless. At no time did any patient become wild or hard to manage. While this series was being run several other patients were given nembutal for analgesia. It was notable that the patients who had received evipal were quieter and more easily managed.

In 3 cases evipal soluble was given without the addition of scopolamine. The results in two cases were very interesting in that they obtained almost complete analgesia without amnesia. All patients were questioned twenty-four hours following delivery. The results classed as good, fair, and poor are shown in Table I.

TABLE I

Analgesia	
Good	36 cases 69%
Fair	10 cases 17%
Poor	7 cases 14%
Amnesia	
Good	32 cases 61%
Fair	8 cases 15%
Poor	13 cases 24%

None of the patients showed the evidences of proctitis that are sometimes seen when drugs are administered rectally.

ANESTHESIA USED FOR DELIVERY

In one primigravida, the entire delivery was accomplished with perfect analgesia and amnesia under 1 Gm. of evipal soluble and $\frac{1}{150}$ gr. of scopolamine given two hours before delivery. At the time of delivery, this patient was drowsy and unresponsive until 1 c.c. of metrazol was given intramuscularly, after which delivery was accomplished spontaneously. The baby cried immediately upon being born.

Another primigravida was delivered with the aid of ½ per cent novocaine, using pudendal block anesthesia. One multipara was given cyclopropane with excellent results. The remainder of the patients received open drop ether at the time of delivery.

EFFECT ON THE BABY

All presentations were vertices except one which was a complete breech. There was one stillbirth which was caused by prolonged labor. The drug can hardly be blamed for the death of the fetus, as the patient was in labor over sixty-two hours, and the last dose of evipal was given forty hours prior to delivery.

There were no gross fetal ill effects encountered in giving the medication even when administered near the end of labor. In one case it was given twenty-nine minutes before the delivery.

No fetal asphyxia was encountered. All live babies cried spontaneously except three in which the cry was somewhat delayed, and

these responded readily to artificial stimulation. In each of these the medication was given five, four, and three hours, respectively, before the time of delivery. No drowsiness was noted after the babies were taken to the nursery. All of them acted quite normally and gave no further concern.

TABLE II

Babies with spontaneous cry	49	92.4%
Babies with delayed cry	3	5.7%
Stillbirth	1	1.9%

DISCUSSION

This series represents 38 primiparas and 15 multiparas to whom evipal soluble was given in hopes of producing analgesia and amnesia during parturition.

The effects upon the mother were quite gratifying. The average length of labor was not prolonged, in fact, the primiparous labors were somewhat shorter than the average. Labor pains did not seem to be diminished in intensity as is often seen with some of the other barbiturates.

It was our experience that all but one patient required some supplementary anesthesia during actual delivery. This is at variance with the results of Siegler and Beris[3] who report 77 per cent of their patients not needing additional anesthesia. Their original dosage was larger than ours.

Since patients vary considerably in regard to their reaction to analgesics, it is difficult to state the correct dosage, much the same as it is difficult to state the exact amount of ether necessary to produce anesthesia. In our opinion, it was preferable to begin with 1 Gm. per rectum and repeat when necessary. We believe our results would have been better if the drug had been repeated in a larger number of the cases.

No untoward reactions were noted in this series, such as the convulsions during delivery as reported by Rosenblum and Webb.[4]

It was our routine, with but 3 exceptions, to give $\frac{1}{150}$ gr. of scopolamine hydrobromide at the time of rectal administration. We are quite sure that this greatly enhances the amnesic action of the drug. In no case, as admonished by Gwathmey[2] was any other barbiturate used in association with or prior to evipal soluble.

It is well to remember that the action of evipal soluble may be reversed by the administration of metrazol if the emergency should arise. This was used with good results in one of our patients, as already stated, who became too drowsy to deliver the baby.

No toxemias were observed in this series. Inasmuch as evipal soluble is detoxified in the liver, as stated by Jones,[5] it would seem inadvisable to consider its use in any toxic case because of placing an additional strain on an already hampered organ.

No excessive uterine bleeding was encountered. Blood pressure determinations were not taken, because it has been amply shown by numerous investigators (Petersen,[6] McNelis[7]) that no significant change takes place in this respect.

The results upon the baby were most gratifying. No cyanosis was encountered. The majority cried spontaneously, and only a small percentage needed artificial skin stimulation to initiate respiration.

CONCLUSIONS

1. In our hands, evipal soluble was a safe and effective analgesic and amnesic when given per rectum during labor.
2. Scopolamine hydrobromide hypodermically greatly enhances the amnesic effect of evipal.
3. When evipal soluble and scopolamine are given during labor, patients do not become as wild and unmanageable as is often seen when other barbiturates are given.
4. Evipal soluble is sufficiently satisfactory to deserve further study in a larger series of cases.

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A REVIEW OF NINETY-FOUR MIXED MESODERMAL TUMORS OF THE UTERUS*

With Report of an Additional Case

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MIXED mesodermal tumors of the uterus are rare and deserve a detailed study. A case of this type was observed at the Kings County Hospital and served as the basis of this study. Such tumors are defined as monodermal in origin, develop from mesoderm and consist of heterotopic and highly malignant tissues. Thus they differ from true teratomas which are of tridermal origin.

HISTORY

Ninety-four cases have been recorded to date. In 1854, Wagner[103] described the first case, but Thiede,[100] in 1877, was the first to emphasize the presence of cartilage and a myxomatous stroma. In 1892, Pfannenstiel[74] recommended calling such tumors "traubiges Sarkom" or botryoid sarcoma, a term still in common usage. Wilms[108] (1899) called them "mixed tumors."

CLINICAL FEATURES

In considering the age incidence, one must differentiate between cervical and corporeal growths (Table I).

*Read at a meeting of the Brooklyn Gynecological Society, October 4, 1940.

TABLE I. AGE DISTRIBUTION

AGE GROUP	CERVIX	CORPUS
0- 9	4	
10-19	6	
20-29	7	
30-39	9	3
40-49	6	9
50-59	3	31
60-69	1	14
70-89		1
Totals	36	58

In the latter group, practically all occur after the menopause, whereas the majority of cervical tumors appear during active menstrual life. Parity exerts no influence on the etiology.

Most authors state that the cervix is the site of predilection, but careful search through the literature reveals 58 cases involving the corpus and only 36 in the cervix, a ratio of 1.6 to 1.

Eight cases have been associated with fibroids. In 6, the mixed tumor arose from the body, while in the remaining 2, the neoplasm was cervical in location. Cox and Benischek[12] reported such a tumor complicating pregnancy, and Reeb and Oberling[81] described one coexisting with a carcinomatous polyp of the fundus.

GROSS APPEARANCE

Cervical tumors usually arise from a narrow pedicle and are grapelike and arborescent, although Jones'[37] case had an annular attachment about the external os. Tumors of the body appear as multiple polyps involving the anterior or posterior fundal walls. Both forms, however, can develop in either site.

On cross section, the tumors reveal cystic cavities intermingled with areas of hemorrhage, necrosis, and suppuration. Cartilage is rarely noted in the gross.[73]

HISTOLOGIC APPEARANCE

These neoplasms are comprised of many elements foreign to the uterus (Table II).

TABLE II. HISTOLOGIC ELEMENTS

	CERVIX		CORPUS	
	NUMBER	PER CENT	NUMBER	PER CENT
"Myxomatous tissue"	27	75.0	41	70.7
Cartilage	20	55.6	35	60.3
Striated muscle	11	30.6	24	41.4
Smooth muscle	7	19.4	20	34.5
Rhabdomyoblasts	2	5.6	8	13.8
Glandular elements	6	13.9	33	56.9
Bone	3	8.3	3	5.2
Osteoid tissue	0	0	4	6.9
Fat	1	2.8	6	10.3
Stroma:				
Spindle cells	27	75.0	55	94.8
Round cells	22	61.1	22	37.9
Giant cells	5	14.0	19	32.8
Associated fibroids	2	5.6	6	10.3

The most common tissue is a loose, myxomatous-appearing stroma which many believe to be embryonal mesenchymal tissue, the anlage for all the other elements. Others contend that it is myxomatous in character, while still others feel that it is mucinous. Its microscopic structure is characteristic: triangular or star-shaped cells with long axionic strands connect with other cells to form a loose network. Their nuclei are either round or oval and usually single.

The second most frequent tissue is hyaline cartilage. It occurs as small islands surrounded with a "perichondrium" of spindle cells. Transition of these cells to cartilage has been noted.[65]

Striated muscle has been noted in 35 of the cases. However, these elements may have escaped notice, since they are sometimes found only after prolonged search and the use of special stains to demonstrate striations. Shapiro and others described large multinucleated cells which they believe are rhabdomyoblasts.

Bone and fat are uncommon. The former has been recorded in 10 cases, while the latter has been observed in only 7.

Most authors describe a pleomorphic sarcomatous stroma, consisting of round or spindle cells intermingled with multinucleated giant cells.

These tumors are extremely vascular. Hemorrhages are common and arise from the thin-walled capillaries.

The neoplasms are always submucosal in location. The overlying epithelium of corporeal growths is columnar in type while those in the cervix are covered with squamous or transitional cells. Should the lining be lacking, local pressure and necrosis are responsible. The surface epithelium rapidly proliferates to form gland spaces, adenomas, and solid cords of cells within the stroma. Cervical and endometrial glands have been observed.

Though nerve tissue and smooth muscle have been described, neither is heterologous to the uterus and consequently cannot properly be considered part of these neoplasms.

As a rule, the tumor is sharply demarcated from the myometrium. Where invasion occurs, it is associated with a sarcomatous-like stroma. In one instance myxomatous tissue penetrated the myometrium.

Metastases are common (Table III) though usually the patients die from operative complications or from cachexia and its associated phenomena.

TABLE III. METASTASES

	CERVIX		CORPUS	
	NUMBER	PER CENT	NUMBER	PER CENT
Total metastases	26	72.2	35	60.3
Pelvis	12	33.3	12	20.7
Abdomen	8	22.2	20	34.5
Lungs and pleurae	3	8.3	8	13.8
Bones	0	0	3	5.2
Inguinal lymph nodes	1	2.8	1	1.7
Local recurrences	18	50.0	16	27.6

Infiltration into the adjoining viscera, such as parametria, bladder, vagina, and peritoneum, is frequent. Nicholson[65] describes the only case with ovarian metastases. The lungs and pleurae are frequent sites for secondary growths. Here they rarely reproduce the parent tumor but, instead, develop as a spindle cell or myxosarcoma. Cartilage has been observed to metastasize three times[30, 31, 61] and striated muscle once.[34]

HISTOGENESIS

The etiology of these tumors is unknown. Wilms' theory of displaced myotome and sclerotome elements is given most credence. He presumes that these structures are included in the Müllerian ducts, as they pass beneath the Wolffian ducts fusing in the midline to form the uterus and vagina. This is substantiated by finding mixed tumors in the base of the bladder, a "site of embryonic organoid tissue fusion and tissue amalgamation"[2] and by the absence of such neoplasms along the Fallopian tubes. The nature of the stimulus to growth is also unknown, but it has been predicated as hormonal.

DIAGNOSIS AND PROGNOSIS

The symptom caused by these tumors is: irregular vaginal bleeding associated with a sanguinopurulent discharge. Pressure symptoms occur if the mass is large or if the tumor has invaded surrounding structures.

TABLE IV. TREATMENT

	CERVIX		CORPUS	
	NUMBER	PER CENT	NUMBER	PER CENT
Total hysterectomy	15	41.7	39	67.2
Vaginal hysterectomy	1	2.8	1	1.7
Supravaginal hysterectomy	0	0	2	3.4
Dilatation and curettage	2	5.6	7	12.1
Amputation of cervix	5	14.0	0	0
Local removal	19	52.8	8	13.8
X-ray therapy	6	13.9	6	10.3
Radium	3	8.3	0	0

These neoplasms are malignant out of all proportion to their histologic appearance evidenced by the high mortality (90 per cent) regardless of therapy (Table IV). The average duration of life following removal is one year. Local recurrences are frequent. Cartilage indicates a highly malignant growth, whereas the presence of fat denotes a more benign one.[15] The longest period of survival was recorded by von Franque:[20] The patient was living and symptom-free ten years postoperatively. Hartfall[30] cites a five-year cure.

CASE REPORT

B. G., a 50-year-old, widowed, nulliparous white woman entered the Kings County Hospital on the service of Dr. Charles A. Gordon on July 18, 1940, complaining of irregular vaginal bleeding for eight weeks associated with an offensive brown discharge for four weeks. The menopause occurred eight years previously. There had been no pain or weight loss. Her past personal and family history were essentially negative. On examination, the patient was well nourished, well developed and had a temperature of 101° F. The head, neck, and lungs were negative. The heart was not enlarged. A short, low-pitched murmur was heard over the pulmonic area. The abdomen was moderately tender throughout and contained a large, firm, movable mass arising from the pelvis. This filled the entire right lower quadrant up to a point three fingerbreadths below the costal margin. Pelvic examination revealed a brown, foul-smelling purulent discharge. The cervix was tender to palpation and admitted one finger. The mass described above, filled the pelvis but a detailed examination could not be carried out because of the pain produced by manipulation. *Laboratory data:* The urine was negative. The white blood cells numbered 11,800 with 82 per cent polymorphonuclear leucocytes and 18 per cent lymphocytes. The red cell count was 3.7 million and the hemoglobin 65 per cent. The sedimentation time was seventy minutes. The clinical impression was "carcinoma of the corpus with infection or septic missed abortion." The latter diagnosis was considered because, on admission, the patient had stated her age as forty years. She was treated as a missed abortion and given 20 gr. of sulfanilamide every four hours for five days. Following this, her temperature and white count fell to normal. Three transfusions totaling 1,100 c.c. were given to overcome the anemia. Two unsuccessful attempts were made to empty the uterus with pituitrin. Six days after admission, on July 29, a curettage yielded considerable tissue, diagnosed microscopically as a mixed mesodermal tumor. On August 15, thirty days after admission, laparotomy revealed the uterus enlarged to the size of a four and one-half months' gestation and the seat of multiple fibroids. A total hysterectomy with bilateral salpingo-oophorectomy was performed. Her recovery was uneventful, and she was discharged from the hospital twenty-one days later. At present, the patient is receiving deep x-ray therapy.

PATHOLOGIC REPORT

Macroscopic.—The specimen consisted of a uterus, practically all the cervix, both tubes and ovaries.

The uterus measured 12 cm. from the top of the fundus to the plane of transsection, 11 cm. transversely at the level of the round ligaments, and 8 cm. in the anteroposterior diameter. The surface was nodular due to numerous, firm, sessile

and pedunculated tumors which varied from 1 to 9 cm. in diameter. On section, all the tumors presented the silvery whorls characteristic of fibromyomas and some of the larger ones revealed small areas of liquefaction necrosis. The segment of cervix measured 3 cm. long. The epithelium of the portio was lacking. The endocervical canal was dilated and lined with a smooth, thin mucosa. Its fibromuscular wall was compressed. On opening the uterus (Fig. 1), the cavity

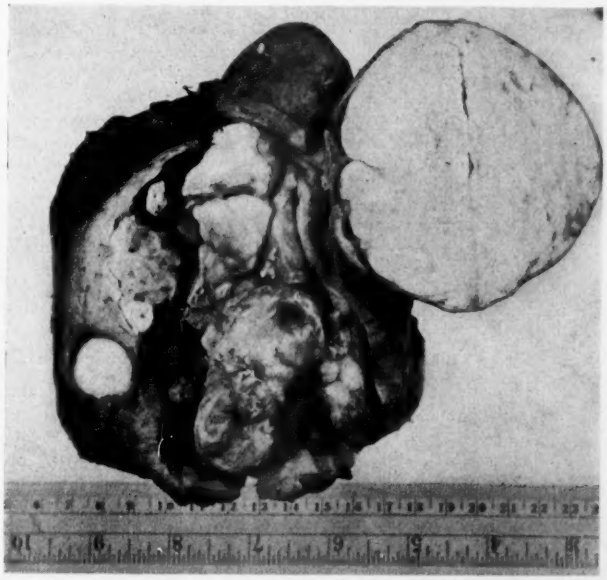

Fig. 1.—The uterus contains many subserous and intramural fibroids. The cavity is filled with varying sized, homogeneous, gray white polyps that are focally hemorrhagic. On the right lateral wall, the tumor is tuberous in character and has invaded the myometrium.

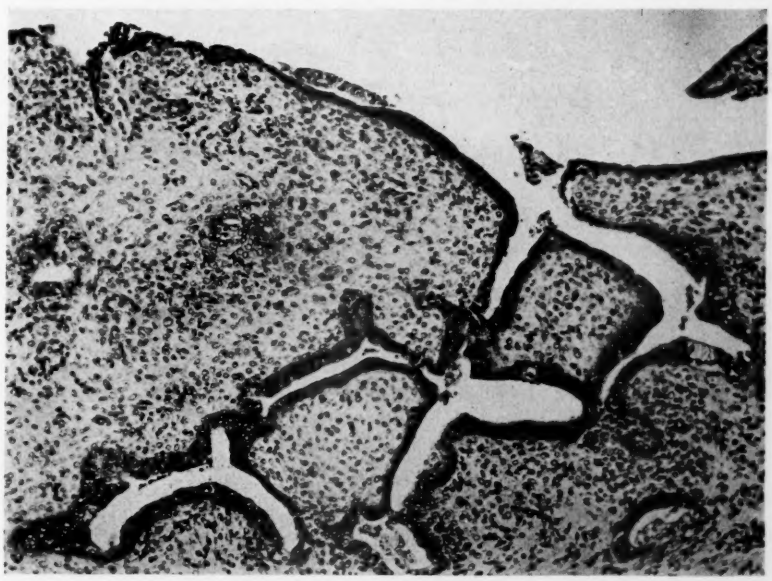

Fig. 2.—The surface presents as small and large polyps covered with tall columnar epithelium. In places, the lining cells are growing down into the stroma and here form glands.

was filled with large, irregular, yellowish white, friable polyps attached to the wall by broad bases which in places penetrated the muscularis up to the serosa. Section through the polyps revealed a homogeneous silvery white matrix, containing small bony or cartilaginous spicules. The myometrium was thin and contained numerous small fibromyomas.

Microscopic.—From the endometrial surface arose many large and small polyps covered with epithelium comprised, in the main, of a single layer of tall cells similar in size, shape, and staining intensity. They contained moderate cytoplasm and a large oval nucleus occupying the basal third (Fig. 2). Focal hyperplasia had occurred, and here they appeared three or four layers deep. In places, the surface epithelium penetrated the stroma to produce varying sized glands lined

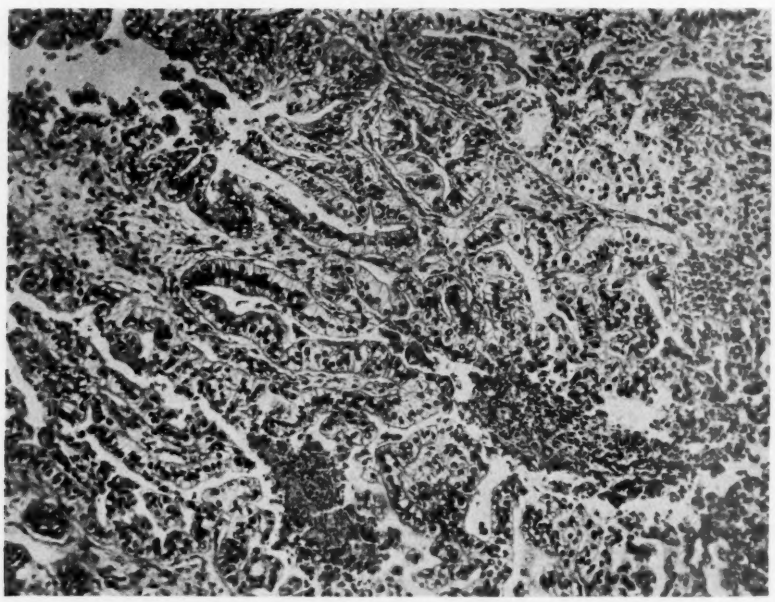

Fig. 3.—The section demonstrates the adenomatoid hyperplasia. The glands are profuse and vary in size and shape. Their lining cells are proliferating rapidly to form papillas which fuse with contiguous ones, producing daughter glands. Many cells and nuclei vary in size, shape, and staining intensity.

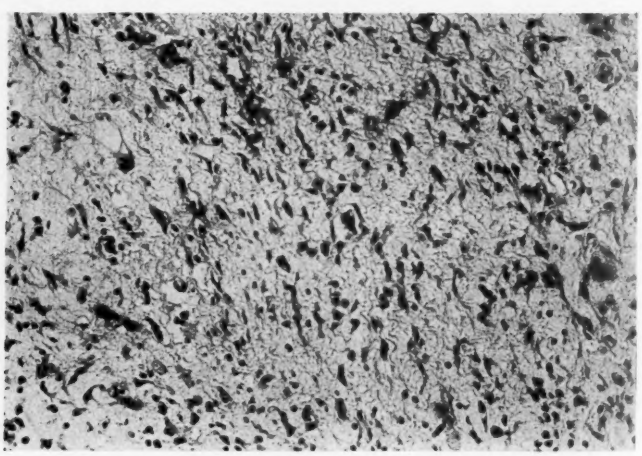

Fig. 4.—The stroma is mesenchymal in nature and comprised of triangular or star-shaped cells from which thin, long axionic processes arise and intermingle with each other.

with anaplastic cells. Papillation and sacculation resulted in the formation of many daughter glands (Fig. 3). The stroma presented a varied picture. In some portions it consisted of compactly arranged small and large oval or spindle cells. In other areas a loose myxomatous matrix was the supporting tissue whose component cell was triangular or star-shaped and connected to each other by long axionic processes (Fig. 4). Multinucleated giant cells rich in chromatin were scattered about (Fig. 5). Parts of the stroma were necrotic and overrun with polymorphonuclear leucocytes. Islands of hyaline cartilage surrounded with a zone of spindle cells formed a "perichondrium" in other sites (Fig. 6). The

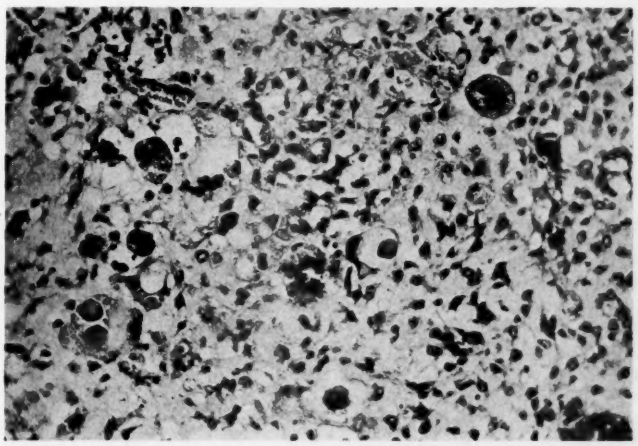

Fig. 5.—In the loose, gray white, embryonal, connective tissue matrix are seen many giant cells. Their nuclei are huge or multiple and rich in chromatin.

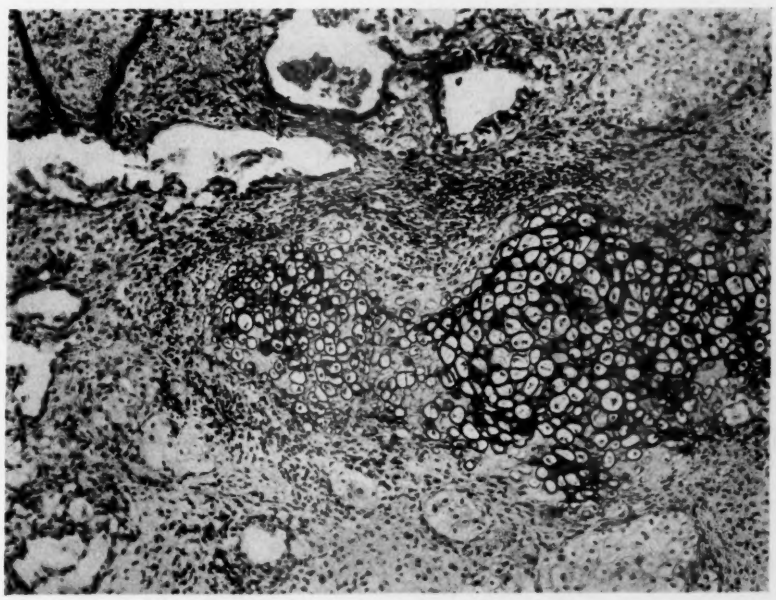

Fig. 6.—Islands of hyaline cartilage surrounded by a compact zone of spindle cells (perichondrium) are seen in the stroma.

myometrium was compressed and contained several encapsulated fibroids presenting hyaline degeneration.

In both tubes and ovaries and cervix, an intense inflammatory reaction was seen. No tumor tissue was encountered in any of these organs.

COMMENT

This case is reported because fibroids occur infrequently with mixed mesodermal tumors. Only 8 have been described previously. The clinical findings are in accord with similar cases as to age, symptomatology, and macroscopic appearance. The microscopic findings agree with the description of other observers. Muscle tissue could not be demonstrated despite the use of special stains as recommended by Glynn and Blair Bell.[28]

No further elucidation of obscure points of histogenesis or therapy can be offered. Radical surgery followed by deep x-ray treatments should prove to be the best therapy, provided early diagnosis is established.

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DIAPHRAGMATIC HERNIA ASSOCIATED WITH PREGNANCY

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DIAPHRAGMATIC hernia producing complications among pregnant women is so uncommon that there are relatively few recorded cases. The patient here reported died during the first stage of her fourth labor from strangulation of the viscera in a diaphragmatic hernia. The case is also unusual in that there had been three previous uneventful deliveries, two of which had occurred after the diaphragmatic hernia had been discovered during laparotomy.

Case History.—G. S. (No. 39-16065), a 23-year-old housewife, gravida iv, para iii, was admitted to the University Hospitals Dec. 10, 1939, at 4:00 P.M. and died at 12:45 P.M. Dec. 11, 1939.

This patient, from 1936 to 1938, had delivered spontaneously three times, each baby weighing from 6 to 7 pounds. The labors were from two to three hours in duration and uncomplicated.

The menstrual history was normal. The last menstrual period began on March 12, 1939, and the expected date of delivery was Dec. 19, 1939.

The patient had been aware of a cardiac impulse in the right side of the chest for several years. An exploratory laparotomy was performed in January, 1937, for "appendicitis." The surgeon was unable to find the appendix and subsequently obtained a roentgenogram of the colon after a barium enema which showed loops of bowel in the left side of the chest.

On admission to the hospital the temperature was 98.4° F.; the pulse rate was 84 and the respirations 20 per minute. The weight was 131 pounds and the height 59 inches. The patient did not appear ill. The organs of the head and neck were essentially normal except that the trachea deviated slightly to the right of the midline. The breasts were enlarged. The chest was symmetrical, but there was a slight delay in expansion of the left side of the thorax. The percussion note was dull over the left lower half of the chest and breath sounds were absent, while the sounds were accentuated over the right side of the thorax. Peristaltic movements were not heard. The rate and rhythm of the heart were normal and there was no pulse deficit. The blood pressure was 125 mm. of mercury systolic and 85 mm. diastolic. The right border of the heart extended to the right midclavicular line, while the location of the left border could not be determined. The uterus reached to within two inches of the xiphoid process, the fetal heart sounds were audible and the fetal head was engaged in the pelvis. Pelvic measurements were normal with an external conjugate diameter of 18.5 cm. and a bisischial diameter of 10.5 cm. Rectal examination showed the cervix closed but partially effaced, and the coccyx was movable. There was moderate pitting edema of the ankles and the reflexes were physiologic.

Laboratory Examination.—The hemoglobin was nine grams (Haden-Hausser) per 100 cubic centimeters and the blood Wassermann and Kline reactions were negative. A sample of urine was not available.

Course in Hospital.—On December 10, at 8:00 P.M., the patient complained of pain in the epigastrium and discomfort in the lower part of the abdomen. It was evident that labor had begun since there was progressive dilatation of the cervix and a bloody "show." During the night uterine contractions continued at five- to six-minute intervals. The patient slept fairly well after being given gr. iii of pentobarbital sodium, but at 8:00 A.M., December 11, some dyspnea associated with moderate pallor of the skin developed. During the next two hours there was increasing cyanosis, orthopnea, dyspnea, and grunting expirations. The pain in the epigastrium became accentuated and radiated to the left lower chest. Fluoroscopic examination at 10:30 A.M. revealed a dextrocardia and what appeared to be stomach and small and large intestines above the diaphragm in the left side of the thorax. A small amount of barium given by mouth disappeared from the esophagus below the diaphragm and then reappeared above the diaphragm to the left of the esophagus, in what was believed to be the lower end of the stomach. Epigastric pain was now severe enough to require morphine. A duodenal tube was inserted into the stomach and approximately two quarts of air aspirated, without relieving the epigastric and left thoracic tympany which had been present since 9:00 A.M. By 12:00 NOON the administration of intranasal oxygen was required to relieve the respiratory difficulty. The patient died suddenly at 12:45 P.M., December 11.

Fetal heart sounds had not been heard for twenty minutes before the mother died. At the time of death the cervix was dilated 7 cm. and the bag of waters was intact. The membranes were ruptured, an incision was made in the anterior lip of the cervix, forceps were applied to the baby in L.O.A., and a normal-appearing stillborn female infant, weighing 3,260 Gm. was extracted.

Autopsy of Mother.—The body was that of a normally developed, well-nourished, white female. The head, extremities, and external surface of the body were not abnormal in appearance except for the presence of one accessory nipple on each side.

The abdomen was distended, tympanitic, and air escaped when the peritoneum was opened. Gross relations in the abdomen were greatly disturbed. The diaphragm on the right side was at the level of the fourth intercostal space, but on the left the dome was inverted and pushed down into the abdomen, so that it was 2 cm. below and parallel to the inferior rib margin.

The liver was crowded to the right. There were two distended loops of jejunum in the epigastrium, floating in 300 c.c. of blood and food particles. The spleen, which was enlarged to 430 Gm., was twisted one turn on its pedicle and lay just to the left of the midline.

When the left side of the thorax was opened, the taut, inverted left diaphragm relaxed. The left pleural cavity contained 450 c.c. of nonsanguineous fluid and food particles, together with a large portion of the stomach, most of the jejunum, all of

the ileum, appendix, transverse colon, and cecum. The latter was in the apical portion of the chest cavity.

The right side of the diaphragm appeared normal, while the left presented an oval-shaped defect, the long axis of which was transverse. The opening was in the posterolateral portion of the dome and measured 13 cm. in circumference. Posterior to the defect there was an intervening slip of diaphragmatic muscle and fascia, measuring 2.5 cm. in diameter. The opening had sharp edges. There was no connection with the other apertures, which were normal. Only a small portion of the cardia and the lower segment of the stomach and pylorus were below the diaphragm; the major portion of the organ, which was bent sharply on itself, was in the lower left side of the thorax. The duodenum was sharply curved in the epigastrium and the near-by loops of jejunum were greatly distended. The remainder of the intestines were in the thoracic cavity, except for the lower part

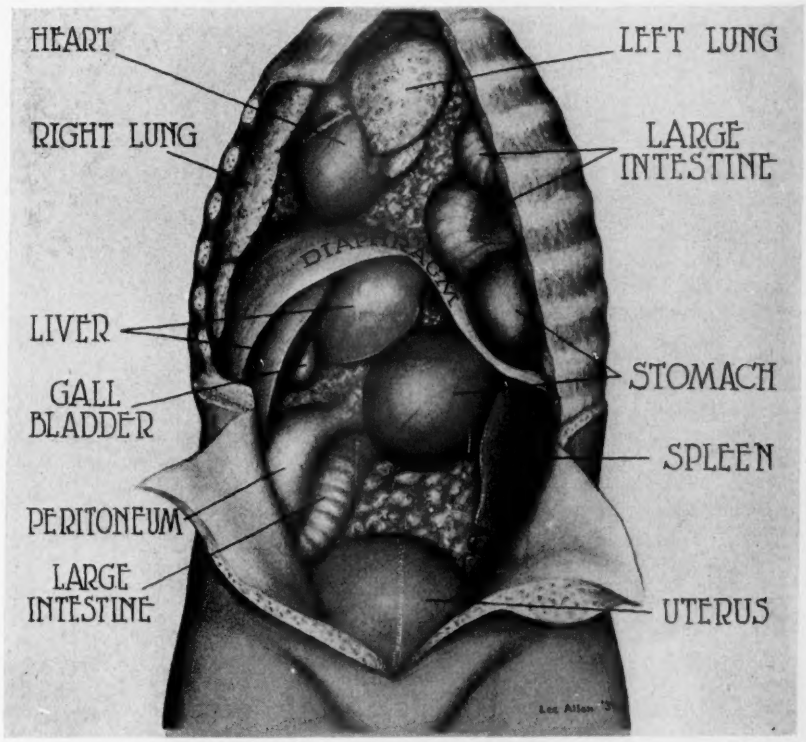

Fig. 1.—Showing the visceral relationships at the time of the autopsy.

of the descending colon which passed back through the defect medial to the posterior cardia and pylorus and lateral to the jejunum. The stomach wall presented a sharply demarcated line of hemorrhagic infiltration at the areas where the cardia and pylorus came in contact with the sharp margin of the diaphragmatic defect. There was a perforation 2 cm. in diameter on the posterior surface of the stomach at the junction of the upper and middle thirds in the region of the edge of the hernia. The intra-abdominal portion of the jejunum showed heavy vascular congestion but no perforation. There was a small amount of bloody fluid in the upper portion of the gastrointestinal tract, and a Meckel's diverticulum, measuring 4 by 2 cm. was present 1.8 meters proximal to the ileocecal valve.

The right pleural cavity contained no excess fluid. The heart and mediastinal structures were pushed far to the right so that the apex of the heart was directly posterior to the fourth costochondral junction on the right. The heart, which had

a patent foramen ovale, was rotated counterclockwise, so that the right auricular appendage was posterior to the remainder of the organ. The almost completely atelectatic left lung lay on and just to the left of the midline, and weighed 140 Gm. There was a long, dense, fibrous adhesion between the base of this lung and the omentum, which was in the left side of the thorax. The right lung was compressed and lay posterior to the heart and other mediastinal structures. It weighed 300 Gm. and was partially atelectatic, especially in the lower lobe.

Examination of the remainder of the abdomen and the pelvis revealed the following: The pancreas, which weighed 100 Gm., contained large areas of hemorrhage, particularly toward the tail. The liver, which weighed 1,250 Gm., the biliary tract, adrenals, kidneys, left tube and ovary, thyroid, and bladder were normal. The ureters were slightly dilated. The right ovary and tube were adherent to the parietal peritoneum in the right lower quadrant of the abdomen. The uterus extended to the level of the umbilicus, and, except for a deep incision 6 cm. in length in the anterior midline of the cervix, showed nothing inconsistent with those of the usual puerperal uterus. There was considerable air under the posterior parietal peritoneum.

The aorta showed slight atherosclerosis. The brain, which weighed 1,140 Gm., and its coverings were not unusual.

A culture of post-mortem blood from the heart remained sterile. The blood urea nitrogen was 14.7 and the creatinine was 1.0 mg. per cent.

Microscopic study of the stomach revealed widespread hemorrhage, particularly in the submucosa in the area of strangulation and around the perforation. There was no inflammatory reaction. The remainder of the gastrointestinal tract was normal except for heavy vascular congestion in the jejunum. The spleen was intensely congested. The pancreas contained large areas of hemorrhage in the parenchyma and some points of early fat necrosis, but no inflammatory reaction. Fatty metamorphosis of the liver and mild chronic pericholangitis were present. The right Fallopian tube revealed mild chronic salpingitis. Sections of the cardiovascular system, thyroid, urinary tract, the remainder of the internal genitalia, and the brain showed no abnormalities.

Anatomic Diagnoses.—Diaphragmatic Hernia, Left: Strangulation of herniated stomach and jejunum with extensive hemorrhage into the stomach wall, possible agonal rupture of the stomach with pneumoperitoneum, pneumothorax, and hydrothorax; torsion and congestion of the spleen; hemorrhage into pancreas with pancreatic necrosis; hemoperitoneum; counterclockwise torsion and shift of the heart to the right; pulmonary atelectasis, partial bilateral; retroperitoneal emphysema; fatty metamorphosis and mild chronic cholangitis of liver; chronic salpingitis; Meckel's diverticulum; patent foramen ovale; polythelia.

COMMENT

Between July 1, 1926, and July 1, 1940, among approximately 190,000 registrations for all causes at the University Hospitals, there have been 45 recognized diaphragmatic hernias, 41 in adults and 4 in infants. In 12 cases the diagnosis was either confirmed or made at autopsy. Thirty-six of the adults were above the age of 40 years and 13 were women. The diagnosis was equivocal in 2 of these women, confirmed at operation in 3, by x-ray studies in 7, and by x-ray and autopsy examination in 1 other. In 5 women the cardiac end of the stomach and in 3 cases the fundus formed the hernial mass. In one other case, both the fundus and cardia protruded into the thoracic cavity, while another showed part of the stomach, colon, and small intestine in the left pleural cavity. Every woman except one had had from 1 to 7 spontaneous deliveries. The histories of the deliveries were recorded as uncomplicated as was also the clinical course of the pregnancies; the only exception to this rule is the case here recorded. Five patients had no symptoms directly attributed to the hernia. Nine individuals had suffered from heartburn and occasional nausea, with vomiting for periods of six weeks to twenty years before the diagnosis was made. Two women gave histories of definite pain associated with deglutition.

According to Rigler and Eneboe[1] the most common diaphragmatic herniation is through the esophageal hiatus; in our group reported here, there were 2 women with a paraesophageal hernia. Rigler and Eneboe made roentgenologic gastric examina-

tions on 195 women in the third trimester of pregnancy. Small hernias through the esophageal hiatus were found in 18.1 per cent of multiparas and in 12.1 per cent of the entire group. In 7 women of this series presenting definite small hernias, the defect was not demonstrable after parturition. These investigators were unable to correlate the symptoms with the presence of the herniations, but felt that repeated pregnancy in young individuals could lead to the production of these abnormalities.

Four fatal cases[2-4] of diaphragmatic hernia diagnosed during pregnancy have been found in the literature. One woman was operated upon for appendicitis at the sixth lunar month, but the appendix could not be located and the hernia was not found. The patient died a few hours after operation, and at autopsy part of the large and small bowel were found incarcerated through the diaphragmatic defect. The other 3 patients had acute symptoms suggesting ileus at the fourth, eighth, and tenth lunar months, respectively. Two of the 3 hernias were not diagnosed before necropsy, while the third was visualized on roentgenographic films. Two of these women (eight and ten months pregnant) became ill with the onset of labor; one died the day after delivery, while the other lived only a few minutes after the third stage was completed. The third patient died in the fourth month as the result of acute strangulation of the hernia.

From the autopsy and the history it is concluded that the case here recorded represented a congenital hernia. The knowledge that she had previously had 3 normal deliveries and 1 laparotomy without complication argued for conservative management during the fourth pregnancy. Moreover, it seems doubtful whether any form of operative treatment would have been of value after acute symptoms appeared. On the other hand, it would seem justifiable to sterilize an individual who has a hernia of this extent to prevent further pregnancies should the hernia be irreparable, a view which is also held by Granzow.[2] It has been definitely proved by Mengert and Murphy[5] that intra-abdominal pressure may increase considerably in the sitting position, and is further accentuated by voluntary muscular effort (Mengert and Murphy[6]) during labor. There is little doubt that the strangulation in this case and in 2 of the others cited was provoked by the increased intra-abdominal pressure associated with the onset of labor.

SUMMARY

Among 13 cases of diaphragmatic hernia found in parous women during the last fourteen years at the University Hospitals, 1 woman died during parturition from strangulation of viscera in a left-sided diaphragmatic hernia. This patient had had 3 previous uncomplicated deliveries.

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OVARIAN PREGNANCY, PRIMARY OR SECONDARY?*

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A PRIMARY, or true, ovarian pregnancy, is one in which the ovum, remaining in the follicle, is there fertilized, develops a sac from the contiguous ovarian tissue, and continues its growth in the follicle. In contrast, a secondary ovarian pregnancy is one in which the ovum is fertilized in tissues, tubal or uterine, outside of the ovary, develops its sac from this extraovarian tissue, and after developing its sac, becomes detached from its parent soil and secondarily attaches itself to the ovary. In the case of primary ovarian pregnancy, the sac if not completely ovarian should be so preponderantly. In secondary ovarian pregnancy, the sac is likely to consist of an admixture of both varieties of tissue, ovarian and non-ovarian, but there should be a predominance of tissues from the site of primary fecundation.

The possible mechanism of primary or true ovarian pregnancy is at the present time a matter for speculation. Caturani[1] predicates as its basis a perioophoritis. A second theory postulates the rupture of a centrally placed follicle into a previously vacated surface follicle.[2] Another theory assumes the retention of Müllerian tissue in the ovary.[3] Sutton[4] formulates a theory based on Sampson's work on endometriosis. To whatever theory we ultimately subscribe, we must accept the existence of two constant factors operating in its etiology, that the ovum remains imprisoned within the cavity of the ruptured follicle, and that the sperm cell finds its way to this particular ovum.

Therefore, one may justly conclude that primary ovarian pregnancy is a rare phenomenon. Many cases reported as primary ovarian pregnancies are excluded by careful reviewers. Thus, Schumann,[5] in 1921, quoted only 43 cases; Sutton,[4] in 1924, accepted only 47 cases; Frank,[6] in 1927, accepted 64, while Wollner,[7] in 1932, discarded 39 of 87 reported cases. More recently, in 1934, Dodek[8] referred to only 52 cases of true ovarian pregnancies. Young and Hawk[9] report one case in a series of 148 cases of ectopic pregnancies, over a period of sixteen years, an incidence of 0.7 per cent. Since then there have been a few reports of additional isolated cases. At our hospital, the case about to be reported is the first noted in a period of over twenty-five years.

CASE REPORT

H. K., married, aged 31 years, was admitted to Gynecologic Service No. 2 of the Mount Sinai Hospital on March 6, 1936, with vaginal bleeding and severe pain in the lower abdomen. Her present illness dates from January 30 of the same year, when after missing a regular period (last regular period Dec. 18, 1935), she was seized suddenly with severe abdominal pain and slight vaginal bleeding. This attack was accompanied by syncope. She was admitted to a neighboring hospital, where a Friedman modification of the Aschheim-Zondek test was positive. A diagnosis of threatened abortion, with a living fetus, was made at that institution. She was given one week of expectant treatment and discharged to the care of her family physician. However, intermittent cramplike pains continued. After four days at home, she returned to the same institution, remaining four additional days under observation, following which she was again discharged. Approximately two weeks later, she was admitted to the Mount Sinai Hospital.

On admission, the patient was found to be well nourished and comparatively comfortable, though complaining of pain and vaginal bleeding. Her temperature was 99.2° F., pulse 100 and of good volume. Tenderness was present over the

*Read at a meeting of the Obstetrical Society of Philadelphia, Pa., May 2, 1940.

entire lower abdomen, more marked over the left lower quadrant. No rigidity or distention was noted. Bimanual examination revealed a soft cervix with a closed external os. The uterus was enlarged to about the size of a two months' pregnancy, partially movable, with tenderness to the right. A tentative diagnosis of intrauterine pregnancy, complicated by pelvic cellulitis and inevitable abortion was made. The following day, on exploration of the uterus, a small amount of well-preserved decidua was found. Later a mass was palpated closely adherent to and to the right of the uterus. Hemoglobin was 68 per cent (Sahli); red cells, 3,680,000; white cells, 11,900; polymorphonuclear cells, 77 per cent. The urine was essentially negative. Because of the continued pain and increasing size of the pelvic mass, a laparotomy was performed on March 25, 1936. The uterus and adnexa were adherent to the large and small bowels. A tuboovarian abscess was found on the right side. On the left side the tube was adherent to and encircled a large, round, bluish, cystlike structure, occupying the region of the left ovary, measuring approximately 12 cm. in diameter. A supravaginal hysterectomy with a bilateral salpingo-oophorectomy was done. The patient made a complete recovery.

PATHOLOGIC REPORT

Macroscopic.—"The operatively removed specimen consists of a supravaginally amputated uterus and adnexa. The uterus measures 8 by 5 by 4 cm. It is firm in consistency throughout. Its wall is intact at all areas. The endometrial layer is thin and moderately injected.

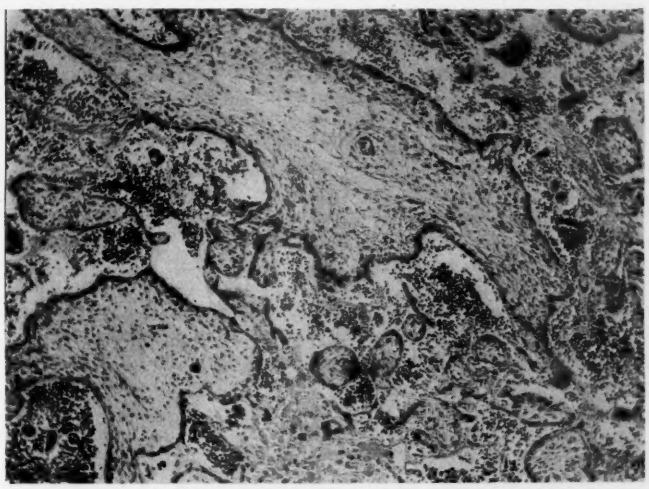

Fig. 1.—Showing chorionic villi. ×60.

"To the right of the uterus is a tuboovarian abscess. The tube is greatly thickened, measuring 7 by 3 cm. Attached to the left side of the uterus and occupying the site of the left ovary is a large roughly globular, dark plum-colored and grayish mass measuring 11 by 8 by 6 cm. A thin layer of clotted blood is present over a small area of its surface. The surface bulges irregularly, particularly over an area 5.5 by 3.5 cm., the latter bulge being caused by a small thin-walled cyst distinct from the major mass. The major mass, on sectioning, consists of a cystic structure, with a moderately thickened wall. It appears on section to be composed of two portions. The lower smaller portion measures 2 by 6 cm. and consists in part of a large corpus luteum, 19 mm. in length. The remainder of this lower portion is a nondescript tissue, inundated with blood.

"The upper portion is separated from the lower by a thin layer of compressed grayish tissue. This upper portion measures 8 by 6 cm. Lying free within its cavity is a fully formed, well-preserved fetus, 8 cm. in length, to which is attached a narrow umbilical cord. Plastered against the lateral, anterior, and posterior walls of this cavity and occupying about three-fourths of its volume are firm,

bluish and grayish masses resembling placental tissue. No membranes can be seen about the fetus nor can the site of attachment of the umbilical cord to the placental structures be determined at this time. The course of the Fallopian tube on the left side has been sharply distorted, passing downward and anteriorly across the anterior surface of the large mass just described. The tube is moderately thickened but appears intact throughout. Its fimbria are congested.''

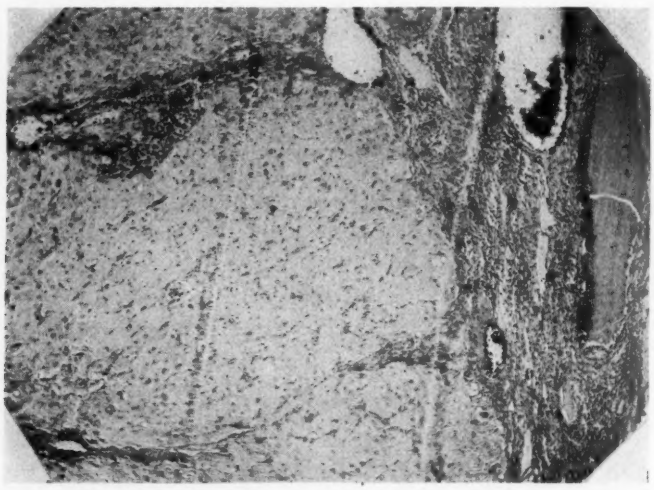

Fig. 2.—Showing corpus luteum and ovarian stroma. ×60.

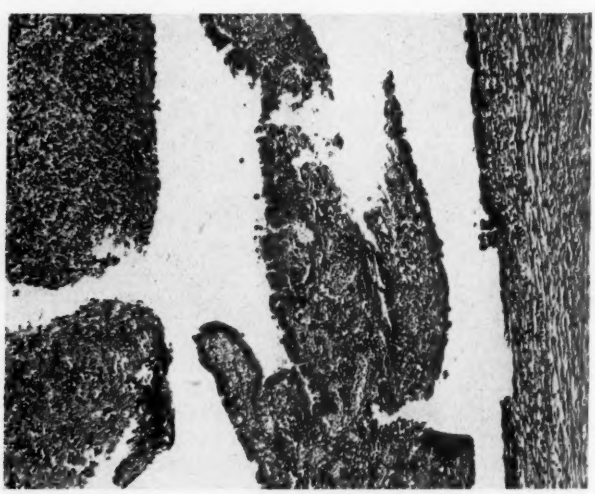

Fig. 3.—Showing portion of wall of sac with epithelial-lined tissue. ×80.

Microscopic.—''The uterine endometrium shows no attached chorionic villi nor any decidual reaction. Both Fallopian tubes show subchronic suppurative processes, involving especially the mucosal layers and the innermost portions of the muscle coats. No decidual reaction is noted in the Fallopian tubes. In the bluish and grayish tissue resembling placenta, observed in the upper portion of the large left-sided ovarian mass already described, are many typical well-preserved chorionic villi, with Langhans and syncytial cell layers (Fig. 1). Other villi are necrotic and hemorrhagic. The corpus luteum described grossly is composed of large lutein cells (Fig. 2). In some of the early sections taken from widely separated

portions of the wall of the sac enclosing the fetus and placental tissue, are collections of ovarian stroma, occasionally containing a small follicle cyst. Graafian follicles are scanty in this ovarian stroma. The latter shows a decidua-like reaction. However, in sections taken later from the wall of the sac there is observed, often in contact with necrotic tissue containing chorionic villi, layers of tissue lined by a low columnar cell epithelium, resembling Fallopian tube epithelium or parovarian epithelium. In some areas this epithelium covers small papillary projections (Fig. 3). In the underlying wall no distinct muscle layers are present, but there are strands of tissue resembling muscle cells. This epithelial-lined tissue is infiltrated with inflammatory cells. It should be stressed that this tissue constitutes a portion of the wall enclosing the products of conception and that these latter products are apparently compressing it and its papillary projections (Fig. 3).''

COMMENT

Obviously, the case reported is that of some form of ovarian pregnancy. The uterine cavity is empty, the left tube is intact, the sac containing a fetus occupies the position where the ovary should be, and the sac is attached to the uterus by the utero-ovarian ligament. Since these gross criteria of Spiegelberg were fulfilled and since a preliminary microscopic report stated that ovarian tissue was found in different and widely separated sections taken from the sac wall, a prima facie case of true ovarian pregnancy appeared established.

Furthermore, from the microscopic studies the additional criteria of both Williams and Norris appeared satisfied. In its entirety, then, this case met not only all the established criteria of ovarian pregnancy but in addition a fetus was found intact in the sac. According to Hunter as quoted by Thro,[12] an embryo was recovered in only 19 instances out of 43 cases.

Having met all the requirements, we were then placed in the anomalous position of having to dispute or, at least, cast a shadow of doubt on the diagnosis of true ovarian pregnancy, because of the presence microscopically in later sections of the epithelial tissue found in different portions of the sac wall as has already been described in the pathologic report.

If this be a primary ovarian pregnancy, the question arises, Why was this epithelial tissue found scattered in different portions of the sac wall? The possibilities are fourfold: contact with the Fallopian tube, contact with an accessory tube, contact with some parovarian tissue, and an endometriosis of the ovary.

We are inclined to consider the possibilities to rest between contact with an accessory tube or contact with some parovarian tissue.

Here then we have a case meeting all the approved criteria of an ovarian pregnancy, and yet there are sufficient anomalous findings which make impossible its unequivocal acceptance as such. The interesting speculation arises, How conclusive are the great majority of cases of so-called primary ovarian pregnancy? Would, as in our case, a more thorough investigation by means of many microscopic sections, have also revealed disturbing findings in many of these reported cases?

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2019 Pine Street

DISCUSSION

DR. EDWARD A. SCHUMANN.—It is extremely difficult to satisfy all the criteria concerning ovarian pregnancy because so often the walls of the sac have

been subjected to pressure and to penetration by blood, so that they are necrotic and partially destroyed.

I belong to the school of thought which was inaugurated by Webster of Chicago and feel that pregnancy cannot occur in the absence of Müllerian tissue. However, the discovery of the presence of endometrial cells and groups of uterine glands in the ovarian tissue itself, has cleared up this matter, so that it is wholly possible for a pregnancy to occur in an ovary, provided a little endometriosis is present. In the case now under discussion I should agree with Dr. Mann that he is dealing with an ovarian pregnancy.

THE EFFECT OF DIETHYLSTILBESTROL AND DIETHYLSTILBESTROL DIPROPIONATE ON POSTMENOPAUSAL VAGINITIS AND SYMPTOMS

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IT IS to be noted that many American writers have found the stillbestrol compounds quite effective as estrogenic agents and giving excellent relief for menopausal symptoms. The so-called toxic effects of nausea and vomiting have almost entirely followed the oral preparations. In contrast to the opinion of Schorr, Robinson and Papanicolaou[1] they have been much less frequent and have extremely rarely followed intramuscular injections. According to the *Lancet*[2] extensive use of stillbestrol in England "does not reveal a high proportion of unpleasant side effects."

MATERIAL

In the present study 111 women have been treated for menopausal symptoms and atrophic vaginitis. Sixty-two were given intramuscular injections of diethylstilbestrol dipropionate (Winthrop). Sixty-eight were given diethylstilbestrol by mouth (in 32 cases, Winthrop's uncoated tablets: in 23, Parke Davis plain capsules; in 8, Lilly's uncoated tablets; and in 33, Lilly's enteric coated tablets).* These women were treated an average of three months each, although 39 were treated more than four months, 5 longer than one year, and 2 continuously for sixteen months.

RESULTS

Of the 108 patients with menopausal symptoms 47 per cent had four-plus improvement, 24 per cent three-plus, 9 per cent two-plus, 2 per cent one-plus and 18 per cent no improvement.† In 14 with no atrophy, 4 showed no improvement in symptoms. These findings indicate much poorer results in the relief of menopausal symptoms than in growth effects on the atrophic vagina. Vascular symptoms were almost invariably relieved. All nervous symptoms at the menopause evidently are not caused by a lack of hormone. From our experience these results do not differ materially from those following the natural estrogens. It does not seem that patients treated with stilbestrol have any different feeling of well-being, as compared with those treated with natural estrogens. No definite tolerance or lack of effect has been noted.

*Because of toxic results reported by some observers, the origin of each material is given. The materials have been generously supplied by the Winthrop Chemical Company, Parke, Davis & Company and Eli Lilly Company.

†Improvement was graded from one to four plus.

Of the 97 patients with atrophic changes in the vagina, 73 per cent showed four-plus improvement, 20 per cent three-plus, 4 per cent two-plus, and 3 per cent no effect. Probably the complete growth effect can be obtained in any case if sufficient material is given. In the 3 per cent without evident effect very slight atrophic changes were present and relatively small doses were given.

DOSAGE

The dosage of these materials has varied most widely. From 0.05 mg. to 5 mg. have been given parenterally, repeated daily or as infrequently as two weeks. By mouth from 1 to 5 mg. have been given daily or at longer intervals. From these studies most satisfactory results have followed these methods: parenterally, 1 mg. each week for two or three weeks, followed by 1 mg. every two to four weeks as long as necessary; orally, 1 mg. daily for six to twelve days, followed by 1 mg. two or three times weekly as long as necessary. Many of the complications described below have followed much larger doses.

COMPLICATIONS

One patient developed a basal cell epithelioma of the nose while receiving 21 mg. by injection over two and one-half months. Any definite causal connection is uncertain.

Postmenopausal bleeding occurred in 12 cases, lasting from one to fourteen days, at times profuse. Later in the study it was evident that often the dosages were too high, although one patient bled several times after very small amounts.

Breast symptoms developed in four patients, three complaining of fullness and one of soreness. No tumors were noted.

A rash over the abdomen appeared in one case early in treatment. After the rash disappeared treatment was resumed. During six and one-half months of further treatment no eruption reappeared.

One patient complained of nightmares while taking oral medication. The nightmares stopped when the medication was discontinued, only to reappear when the oral stilbestrol was resumed. Later injections of the dipropionate were accompanied by no nightmares and relief of nervous symptoms.

Nausea and vomiting occurred in two patients after parenteral injections. In each case the symptoms followed 5 mg. injections and were not present during subsequent treatment with smaller dosages.

Nausea and vomiting followed oral medication in 17 cases (25 per cent of those receiving oral material). In 10 of these there was only nausea and no vomiting. In 5 the nausea wore off as the drug was continued, and in a sixth nausea appeared only after twenty days with 1 mg. daily. In 7 cases there was also vomiting. An analysis of the different commercial products shows these symptoms occurred as follows: 10 in 32 with Winthrop's plain tablets, 7 in 23 with Parke Davis plain capsules, 1 in 8 with Lilly's plain tablets, and 1 in 33 with Lilly's enteric coated tablets.

The enteric coated oral material is of particular interest. In 33 cases, only one had nausea and vomiting. This patient had had frequent nausea and vomiting before taking the medication, which continued after the drug was stopped. No other patient offered any digestive complaint. In 3 of the above patients with nausea and vomiting from the uncoated material, such symptoms disappeared when the enteric coated drug was given.

The fact that enteric coating apparently prevents nausea and vomiting from the oral preparations may lead to a different consideration of this drug. At the present time the great fear of toxic reactions has prevented its general use. Certainly the most common toxic reaction has been of gastrointestinal origin. If these symptoms can be pre-

vented by such a simple method as enteric coating, the seriousness of the reactions could not be great and the main objection would be overcome. No doubt this potent drug, as any other, may be harmful if given excessively. At the present time there seems to be no serious harm in its therapeutic use and certain advantages in its oral use and low cost.

SUMMARY

1. One hundred and eleven patients with menopausal symptoms and atrophic vaginitis have been treated with diethylstilbestrol and diethylstilbestrol dipropionate for an average of three months each.

2. The results seem entirely comparable with the natural estrogenic hormones.

3. Nausea and vomiting from oral preparations apparently may be relieved if the material is enteric coated.

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DERMOID CYSTS OF THE OVARY

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(From the Department of Pathology, Cook County Hospital)

THIS is a study of dermoid cysts of the ovary removed at operation at the Cook County Hospital. In the files of the surgical pathology laboratory covering a period of ten and one-half years, from July, 1928, to December, 1938, a total of 121 cases of dermoid cysts of the ovary is listed. These dermoid cysts comprise 14.9 per cent of all benign and malignant ovarian tumor studies, excluding enlargements of the ovary due to simple follicular cysts and corpora hemorrhagica. Unfortunately only 103 of the histories of the above 121 cases were obtainable. The remainder of the paper is a study of these 103 cases.

Simple dermoid cysts or benign cystic teratomas have been well known for many years and were thoroughly reviewed by Miller[1] in 1937. However, Miller collected only 953 cases in which the site of the tumor was given. (Complete references to this subject can be found in Miller's paper.)

The average age incidence in this series (Fig. 1) is 32.8 years, which is similar to the figure given by Kouchy[2] in this country as 38.37. There were 78.4 per cent of the cases which occurred between the ages of 20 and 45 years, with a peak between 35 and 39 years. Marital histories were obtained in 88 cases, of which 31 denied pregnancy and 57 had been pregnant a total of 159 times. From these pregnancies there had been a total of 115 live births. Of the 57 cases there had been an average gravidity of 2.8 and an average parity of 2.0.

The race of the patients is stated in 76 cases, of which 55.3 per cent were colored and the rest white.

The location of the tumor was known in 87 cases, of which in this series, 58.6 per cent were in the right ovary, 33.3 per cent in the left ovary, and 8.1 per cent were bilateral. In the 953 cases collected by Miller, 45.0 per cent were in the right ovary, 39.2 per cent in the left ovary, and 15.2 per cent bilateral.

Absolutely no correlation could be found between the size of the tumor, the age of the patient, the duration of symptoms, or the number of times the patient had been pregnant.

The presenting symptoms (Table I) were chiefly of pain, usually in the abdomen, or of swelling of the abdomen. These were found in 49.4 and 29.2 per cent, respectively. The next most frequent complaint was menstrual changes, and was given in 15.7 per cent of the cases.

TABLE I. CHIEF COMPLAINT ON ADMISSION

	NUMBER OF CASES		PERCENTAGE OF CASES
Pain in the abdomen	41	44	49.4
in the back	3		
Swelling or tumor of abdomen	26	26	29.2
Menstrual changes			
Menorrhagia or bleeding	6	14	15.7
Dysmenorrhea	2		
Amenorrhea	4		
Irregular menses	2		
Other complaints			
Vaginal discharge	1	5	5.6
Pregnancy	2		
Prolapse of the uterus	1		
Urinary symptoms	1		
Total	89		99.9

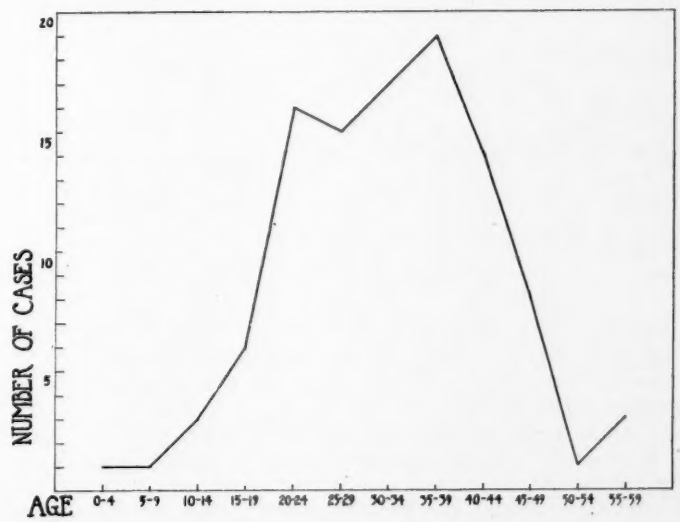

Fig. 1.

The dermoid cysts were correctly diagnosed preoperatively (Table II) in only 3.1 per cent of the cases, but the diagnosis of ovarian tumor or cyst was made in 30.9 per cent of the cases. The other common preoperative diagnoses were uterine fibroids in 39.2 per cent, and chronic salpingitis or tuboovarian abscess in 13.4 per cent. Of the three cases diagnosed preoperatively, one was in a five-year-old girl with an abdominal mass 9 cm. in diameter present for one month and a history of abdominal cramps for one year. The second was made in a 29-year-old woman with a similar sized mass present for four years. The third was in a 21-year-old woman who had had a large abdominal mass for two years. In all of these cases the tumor was large, and in the two adults had been present for two and four years.

X-ray has often been used for the visualization of teeth or bone in these tumors, but was not used in any of these cases.

TABLE II. PREOPERATIVE DIAGNOSES

	NUMBER OF CASES		PERCENTAGE OF CASES
Ovary			
Dermoids	3	3	3.1
Other tumors, usually cysts	30	30	30.9
Uterus, fibroids	38	38	39.2
Fallopian tubes			
Chronic salpingitis and chronic abscesses	13	16	16.5
Ectopic pregnancy	3		
Appendicitis	4	4	4.1
Other conditions			
Tumor, location not stated	1	6	6.2
Pelvic peritonitis	1		
Hematometria	1		
Prolapse of the uterus	2		
Pregnancy	1		
Total	97		100

TABLE III. CAUSE OF SYMPTOMS

	NUMBER OF CASES		PERCENTAGE OF CASES
Ovary			
Dermoid mass	29	37	38.1
strangulation	8		
Other tumors	10	10	10.3
Fallopian tubes			
Chronic salpingitis or hydrosalpinx	15	15	15.5
Uterus			
Fibroids	20	20	20.6
Other conditions as acute appendicitis and prolapse of the uterus, etc.	7	7	7.2
Symptoms not due to any one cause	8	8	8.3
Total	97		100.0

The cause of the symptoms (Table III) as far as could be determined was the dermoid mass in 29 out of a total of 97 instances, and the symptoms were caused by strangulation of the mass in 8 others, making a total of 37 cases, or 38.1 per cent, in which symptoms could be directly traced to the dermoid cyst. Coincident salpingitis or hydrosalpinx was the cause of symptoms in 15 cases; other tumors of the ovary, usually simple serous cysts in 10, and fibroids of the uterus caused the symptoms in 20 instances. In 7 other cases dermoids were found incidentally to such other conditions as acute appendicitis and prolapse of the uterus, while in the remaining 8 cases, the symptoms did not seem definitely related to any one cause.

In conclusion, although dermoid cysts are one of the commonest ovarian tumors, they are seldom diagnosed preoperatively, because of the indefinite symptoms they produce. Very often they are incident to other pelvic conditions.

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POST-PARTUM STERILIZATION

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DURING the past twenty-eight months, 165 post-partum patients have been sterilized at the Presbyterian Hospital at San Juan. This is the largest series yet reported. Recently Adair and Brown reported 50 and Hewitt and Whitley 100 cases; both groups were selected to insure freedom from infection and ease of operation. Our series has been relatively unselected and done at varying intervals of time post-partum.

It is rarely convenient for us to operate immediately following delivery. For this reason the delay in almost every case was due to the convenience of time rather than the condition of the patient. Of the 165 patients, 127 were operated upon in the first twenty-four hours, 33 in the second twenty-four hours, 3 on the third day, one on the fourth day, and one on the fifth day, an eclamptic patient unconscious for four days and markedly toxic. The average length of time was 17.5 hours.

Patients for whom sterilization was recommended were almost entirely ward patients. Private patients usually have access to and are more able or willing to use other less permanent forms of contraception. As soon as it became known that we were doing this type of sterilization, we were deluged with requests, and if for no other reason than self-defense, we have been very strict in the indications. These have been as varied as any given in previous papers, as is indicated in Table I. The greater the parity the less we require of good medical

Table I. Primary Indications

Heart disease	4	Contraception for future operations	9
Toxemias of pregnancy and hypertension	6	Markedly contracted pelves	8
Syphilis	4	Epilepsy	3
Previous section	1	Schistosomiasis	1
Multiple pregnancies	63	Chronic tropical lymphangitis	3
Pulmonary tuberculosis	5	Social and economic indications	56
Recurrent pyelitis	2		

indications. However, patients for whom sterilization was recommended due to multiple pregnancies or economic and social considerations had also as a major concurrent consideration the danger of additional pregnancies to their health and life. Due to the local conditions of gross over-population, increasing at the rate of 30,000 a year, or 9 per square mile per year, and the inability of the island to produce the bare necessities of life, the fear of endangering the future population was reduced to a minimum.

The average age of all patients sterilized was 27.83; the average parity at time of operation was 5.04. The number of dead babies was 0.68 each, spontaneous abortions 1.0, and induced abortions 0.3. Nine patients had had previous lower abdominal operations, and one had had drainage of the cul-de-sac. Thirteen patients had a hemoglobin of 50 per cent or less at the time of operation. Seventeen patients were medically induced.

Only two patients who would have been sterilized were refused operation due to their condition. Both were grossly infected on admission to the hospital and ran a long febrile post-partum course. Two others were postponed three days because of fear of infection.

Preoperative medication was given routinely to the patients. Three grains of nembutal were given one hour before operation and ¼ gr. of morphine with $\frac{1}{150}$ gr. of scopolamine three-fourths of an hour before operation. The amounts varied somewhat depending on the size of the patient. Almost none of the patients had any memory of leaving their room, and they usually slept through the entire operative procedure. Postoperatively only codeine and aspirin were given, and we have not noticed that these were given with much greater frequency than to other post-partum patients.

Routinely, operations were done with local infiltration anesthesia of 0.5 per cent novocaine. A short paramedian incision was made just below the level of the umbilicus and the tubes brought into the field by hooking a finger over the round ligaments and rolling the uterus from side to side. In each case the tube was grasped in its midportion with an Allis forceps and clamped across the loop gently with a large Kelly forceps about 1 cm. from the Allis. A single tie of black silk was placed about the loop and usually an additional tie was placed through the meso-salpinx and around the tube in the tied-off loop of the tube. We endeavored to tie the first tie snugly but not so tightly as to cut the peritoneum. Closure of the abdomen was made with silk. Twenty or more minutes were usually required to complete the procedure.

Often we found a greater or less degree of edema of the Fallopian tubes, so that they resembled the round ligaments. Twice interns had attempted to tie the round ligament before attention was called to their error. On three occasions we have noticed thrombosed veins in the broad ligaments, but only once did these give later trouble. The gut is frequently not seen and only rarely does the patient cause trouble by pushing out a loop of gut. There is a minimal disturbance of tissue and no intra-abdominal bleeding.

For economic reasons and convenience to the patient, other relatively minor operations may be easily done while the patient is under the influence of deep sedation. One umbilical and two inguinal hernias have been repaired at the same time, and all patients were afebrile postoperatively. On one occasion where symptoms of acute appendicitis were presented, an appendectomy was done at the time of sterilization, in which case the patient was febrile the first four postoperative days. However, appendectomies would eventually lead to trouble and should certainly be discouraged at this time. Almost never do we do any exploration, however slight.

Using the morbidity standard advocated by the American Committee on Maternal Welfare, the incidence of febrile morbidity of all patients was 18.3 per cent. Table II shows rather definitely that the lowest morbidity is found in patients operated

TABLE II. SUMMARY OF MORBIDITY COMPARISON

HOURS POST PARTUM	PATIENTS OPERATED	PATIENTS FEBRILE	PER CENT FEBRILE
0–6	29	4	13.8
6–12	44	6	13.6
12–18	36	6	16.6
18–24	18	4	22.6
24–30	19	4	21.0
30–72	19	6	31.5

upon in the first few hours after delivery. The incidence in 73 patients operated upon within the first twelve hours after delivery was 13.7 per cent. This compares

favorably with all of our post-partum patients during this same period, of whom 18.6 per cent were morbid. However, if we compare it with only the multiparas not sterilized during this period, the comparison is not so favorable, as these patients had only a 9 per cent morbidity. We are unable to account for this, considering the lack of symptoms relative to the operation, but can attribute some of it to urinary tract infections abetted by the dehydration of the patient on the day of the operation. Only three patients remained in the hospital more than twelve days. One of these had phlebitis of the leg and was discharged on the thirty-fourth day. Another had phlebitis of the veins of the broad ligaments and was discharged on the twenty-seventh day. In this case thrombosis of the veins of one side of the broad ligaments was observed at the time of operation and pain developed on this side first. These are the only two patients having thrombosis or phlebitis in this series. They were operated upon twelve and twenty-two hours after delivery, respectively. The third patient remained in the hospital fifteen days because of an attack of cholecystitis and cholelithiasis. None of the patients were at any time critically ill and in none could the infection be definitely attributed to the operation itself, although in the case of the patient having pelvic phlebitis, the sterilization was undoubtedly a large contributory factor. Of 11 patients who had vaginal examinations or manipulations, 5 were febrile; however, the indication for manipulation may have contributed also. The average postoperative stay before discharge was 9.4 days. Of 4 patients complaining of some degree of pelvic tenderness several weeks following delivery, 3 had been febrile in the hospital. There were no wound infections and there were no deaths.

Of the 165 patients sterilized, we know of 3 who have become pregnant again at intervals of three, four, and five months following operation. We reoperated upon two of the patients after the second delivery, removing the proximal portions of the Fallopian tube for examination and found that in one case a fistula had developed to the lumen of the proximal portion and in the other the atrophy of the tied-off portion was incomplete. Madlener suggested that the tie be made toward the outer portion of the tube, and findings in the two above cases would indicate this, as in both the tubes were tied quite close to the uterus. While in other patients on whom we have reoperated for other reasons and who have not become pregnant, the tie was found in the middle or outer portion with a section approximately 1 cm. long in which the tube was completely atrophied. No adhesions have been found either to the parietal or visceral peritoneum in any of these reoperated cases.

CONCLUSIONS

The operation in general is a safe procedure, and easily accomplished with no unusual discomfort to the patient nor danger to her life. As has been pointed out by previous writers and as is borne out by these statistics, the sooner the operation is done following delivery the lower will be the incidence of fever. In addition, the operation is more easily done when the uterus is large and the intestines are held away from the incision by its mass.

The greatest deterrent to pointing out the ease and safety of this operation is, that it may be too facilely performed on the post-partum mother who says, "no more babies," resulting in future sorrow and regret by the patient and an increased shortage of children in future generations.

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AN "AUTOMATIC" POST-PARTUM UTERINE PACKER*

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(From the Department of Obstetrics and Gynecology, University of Georgia School of Medicine)

IN FEW other surgical procedures is time quite so much a vital factor as in the operation of uterine packing for post-partum hemorrhage. In the excitement of sudden and severe bleeding, the sterility of the procedure is often neglected and the pack is dragged over unsterile portions of the body. Furthermore with the usually available instruments, the introduction of the pack into the top of the fundal cavity is difficult and often unsuccessful, and the uterus bleeds above the gauze, nullifying the beneficial aspects of an otherwise most effective and life-saving procedure. Of course, the administration of pituitrin preparations and of ergonovine intravenously if necessary, after the birth of the portion of the greatest diameter of the child, should be more or less routine.

To facilitate the obstetric operation of uterine packing for post-partum hemorrhage so that within one or two minutes the pack may be introduced aseptically into the very apex and horns of the uterine cavity, the herein described instrument is offered. It is a large size modified Holmes packer with, as an integral part, a container for the requisite gauze pack. The length of the tube is about 6 inches and its diameter ¾ inches. The large hole is for loading the pack and the small ones (advised by a former resident, Dr. W. W. Coppedge) are for introduction of an antiseptic as hexylresorcinol S.T. 37 to reduce bacterial growth after the pack is in place.

The Method of Use.—The device loaded, wrapped in towels, and sterilized in the autoclave is kept sterile. When puerperal uterine bleeding is severe, the obstetrician introduces his sterile-gloved left hand high into the uterine cavity. It is of advantage to have someone to hold the fundus through the abdominal wall. The nurse unwraps and presents the packer. The obstetrician introduces his right index and middle fingers into the finger holds and his thumb into the ring of the obturator piston. The introducing tube is then gently pushed through the vagina and cervix into the hollow of his left hand in the uterine cavity. The pack is then displaced by the obturator into the uterine cavity. At the same time if the body of the packer is moved from side-to-side, the pack is snugly and entirely aseptically inserted across the top of the uterine cavity. All of the pack is expelled gradually, elevating and filling the uterine cavity and upper portion of the vagina. It may be removed in twenty-four to thirty-six hours.

While the name "automatic uterine packer" is a misnomer it is of advantage in that it affords an accurate mental picture to the nurse and obstetrician for its use on short notice.

Notwithstanding routine use of pituitrin and ergonovine, it has been found from a study of the records that about one in 200 women in labor bleed following delivery enough to be classed as post-partum hemorrhage.

The following are case reports of 11 such patients. Post-partum hemorrhage from this study is more common in white than in negro women.

CASE 1.—White woman, aged 24 years, para iii, well-nourished with mild toxemia of pregnancy, delivered her third child, 7½ pounds, at home. She bled too much (the students estimated 2 liters), and continued to ooze and was sent to the hospital where upon pressing upon the fundus a blood clot the size of a fetal head was expelled. The uterus failed to remain firm. She became nauseated and vomited, and her skin became clammy, and the pulse rapid. She was taken to the delivery room and prepared for operation. No tear was found in the perineum or cervix. The

*Manufactured by the Sklar Instrument Co., Long Island City, N. Y.

uterine cavity was packed with sterile gauze with the use of the automatic packer. The pack was removed in twenty-four hours and no bleeding ensued.

Her temperature on admission was 102° F. After the insertion of the pack she was given a transfusion of 500 c.c. of citrated blood. Her temperature the second day went to 103° F., not quite so high the third day, and thereafter fell rapidly to normal. She was dismissed as recovered on the seventh day.

CASE 2.—White woman, aged 34 years, well-nourished para v, had had a fairly normal pregnancy, but she went into labor with transverse presentation breech left, head right, with left arm prolapsed through dilating cervix. She was ordered treated by large Voorhees' bag insertion to be followed by podalic version and extraction. However, the cervix was found to be fully dilated, consequently the child was then turned and delivered. No lacerations of the fundus, cervix, or perineum were found. In spite of pituitrin and ergot and constant massage of the uterus, she continued to bleed for two hours, when she was returned to the delivery room and a fundal pack was inserted by use of the automatic packer. The pack stopped the bleeding entirely, and was removed in thirty-six hours. At no time did her temperature rise above 98.6° F. Inasmuch as her hemoglobin remained high, 12 Gm. per 100 c.c., she was not given a transfusion.

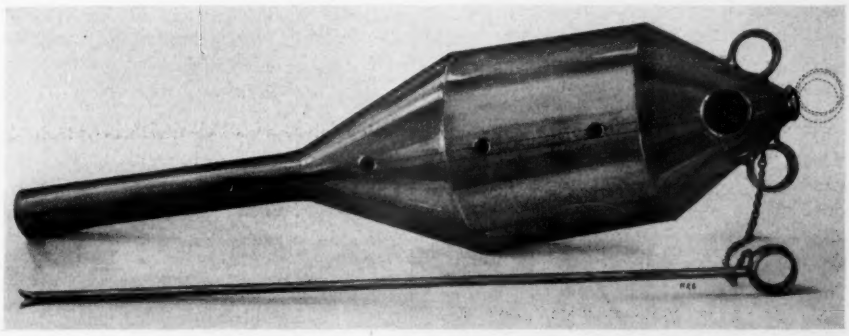

Fig. 1.

CASE 3.—Negro woman, aged 17 years, para ii, while in the emergency room delivered a 7-pound, 12-ounce baby without apparent injury to her cervix or perineum. She continued to bleed vaginally in spite of repeated administration of pituitrin and ergot preparations and massage of the uterus. The following note four hours post partum is self-explanatory: "Blood pressure 98/60; continues to ooze from vagina —has had ergotrate intravenously, etc. So under sterile precautions cervix visualized, seemed OK, but continuous oozing was seen coming from os. Packed with automatic uterine packer intrauterine and intravaginally. Blood pressure 65/20." She bled no more and her blood pressure returned to normal. The pack was removed in thirty-six hours. Her temperature, while the pack was in place, rose to 100.4° F. once and 102° F. on the third day. After this, the temperature rapidly returned to normal. Her hemoglobin was recorded as 6.5 Gm. and her red cells as 2,440,000. She should have had a transfusion but went home otherwise recovered on the twelfth day.

CASE 4.—White woman, aged 24 years, slight obese constitutional type, with mild toxemia, was sent into the hospital from home delivery service two hours after completion of a long labor since when there had been constant bleeding vaginally. She was in mild surgical shock. She was prepared for operation, and her uterus was found to be full of clots which were removed and the fundus packed with use of the automatic packer. She was then given 500 c.c. of citrated blood. The pack was removed in thirty-six hours, and no bleeding followed.

She developed no fever and went home on the fifth day with not quite 4,000,000 red cells per c.mm. and 65 per cent hemoglobin.

CASE 5.—White woman, aged 22 years, obese type, primipara, was in labor a total of twenty-six hours and thirty minutes with a long second stage. She had a large

pelvic inlet AP 12 cm., transverse 14 cm., and good outlet, but the posterior hand prolapsed alongside of the cheek. She was delivered by low forceps from an L.O.A. presentation. The child, weighing 7 pounds 3 ounces, was resuscitated with difficulty but lived. The placenta was promptly expelled, but there was considerable bleeding vaginally in spite of pituitrin, ergot, and uterine massage. A pack was inserted with the use of the automatic packer, and she recovered without further bleeding. She had no fever at any time throughout her stay of one week.

CASE 6.—White woman, aged 22 years, well nourished, para ii, was sent into the hospital because of prolonged first stage of labor, twenty-six hours and forty-five minutes. The second stage was very short, and she spontaneously delivered an 8 pound 4½ ounce normal female child.

Immediately following, in spite of several ampoules of pituitrin and ergot preparations, she had severe vaginal bleeding and developed a state of surgical shock with a blood pressure 60/40 and cold and clammy skin. Her uterus was packed with the automatic packer, and she was given two transfusions of 500 c.c. and 300 c.c., respectively. She recovered rapidly and went home on the seventh day. Her highest temperature was 100° F. once each on two days.

CASE 7.—White woman, aged 31 years, para ii, well nourished, had a short first stage and a rather long second stage, over two hours. The large head was then found to be in R.O.P. It was normally rotated to R.O.T. and Kjelland application of Kjelland forceps made, and with two pulls of forty-five seconds each at intervals of one and one-half minutes, the 7 pound 11 ounce baby was easily delivered. There was a first degree tear of the perineum, which was repaired. She then bled profusely from the fundus which was firmly packed with the use of the automatic packer. While the pack was in place, her temperature was 100° F. When it was removed at twenty-four hours, the temperature remained normal, and she went home on the third day. The attending physician stated that near the end of the first stage of labor the patient had been given 3 mm. of pituitrin subcutaneously.

CASE 8.—White woman, aged 27 years, para iii, delivered a 9-pound baby on the outpatient service and was sent into the hospital because of retained placenta. At the end of five hours this was removed manually from the upper posterior wall, following which there was a tendency for the fundus to bleed. There was no evidence of injury. Her blood pressure dropped to 80/60, and the uterus was packed with the use of the automatic packer. Following this, she was given three blood transfusions, totalling 1,000 c.c. The pack was removed at thirty-six hours, and there is no record of any subsequent bleeding. While the pack was in place, the temperature was normal. After its removal, fever of 101° F. was observed once on each of two days. When she was dismissed on the tenth day, she had 3,520,000 red blood count per c.mm.

CASE 9.—Negro woman, aged 20 years, of medium constitutional type, after normal labor, delivered a 7-pound 5-ounce baby by breech presentation. Notwithstanding the administration of pituitrin and ergot preparation, she bled profusely from the uterus. There was found slight injury to the cervix and perineum. Her uterus was packed with the use of the automatic packer. At the time of inserting the pack, her temperature was 102° F.; pulse rate, 128. The pack was removed at the end of thirty-six hours, and there was no bleeding. She recovered rapidly and went home on the sixth day.

CASE 10.—White woman, aged 22 years, medium constitutional type, had a normal delivery of a 7-pound 12½-ounce baby. Following normal delivery of the placenta, there was profuse vaginal bleeding. There was some laceration of the cervix which was repaired by catgut sutures. The fundus was packed, using the automatic packer, and the pack controlled the hemorrhage completely. It was removed at the end of twenty-four hours, and the patient fully recovered without fever and went home on the third day.

CASE 11.—White woman, aged 20 years, in her second pregnancy went into premature labor with a transverse presentation and a prolapse of a fetal arm. She was

anesthetized and delivered by version and rather difficult extraction. The baby, which was stillborn, weighed 4 pounds 12½ ounces. Following delivery, the uterus bled profusely in spite of pituitary and ergot extracts and was packed from the automatic uterine packer. This completely controlled the bleeding and the pack was removed at the end of twenty-four hours, following which the patient had no elevation of temperature above normal. She went home on the third day.

CONCLUSIONS

1. All of these cases were failures in regard to control of uterine hemorrhage by oxytocic pituitrin and ergot preparations, even intravenously administered.
2. In each the bleeding was completely and immediately controlled by this method of packing.
3. In none was there evidence of any infection produced.
4. An easily comprehensible, compact, and efficient device is described for the performance of this frequently neglected life-saving operation.

SIAMESE TWINS (THORACOPAGIC) COMPLICATING TRIPLET PREGNANCY*

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(From the Broad Street Hospital)

THIS congenital abnormality is so rare that a careful review of the recent literature shows only one similar case report. Ilberg[1] reports a case seen at the State Woman's Clinic at Dresden, in March, 1939.

This was a 41-year-old, para ii, delivered by a midwife of stillborn Siamese twins, followed by a third fetus which lived for twelve hours. All were at term, all females and having one placenta for the twins and one for the single fetus.

We are, therefore, reporting our experience because of the rarity of such cases and in view of the fact that we delivered one living child, after a very difficult labor.

Mrs. H. T., an Italian housewife, aged 25 years, registered in our prenatal clinic in July, 1939. On admission she was approximately four months pregnant, with no complaints. Last menses occurred March 19, 1939. Calculated date of confinement was Dec. 26, 1939.

Family history and past personal history were essentially negative. Physical examination revealed no pathology.

The height of the fundus was 20 cm. Pelvimetry was normal.

Her prenatal course was uneventful and she was admitted to the hospital in labor on Nov. 27, 1939, at 11 A.M., one month before the calculated date of confinement.

Pains began at 9:30 A.M. on November 27, and the membranes ruptured at home.

On admission, physical examination was normal except a blood pressure of 152/100. Urinalysis showed a heavy trace of albumin.

Abdominal examination revealed the presence of twins, R.S.A. and L.S.P. Two fetal hearts were auscultated, one on the right side near the umbilicus and the other laterally on the left side. Rectal examination revealed a breech presentation with no cervical dilatation.

The patient was considered a normal case for spontaneous delivery (blood pressure subsequently dropped to 130/90) and was allowed to progress in this manner. At 10 P.M. after approximately eleven hours in labor she was transferred to the delivery room with a footling presentation.

*Presented at a meeting of the Obstetrical Society of Philadelphia, October 3, 1940.

Vaginal examination revealed the cervix completely dilated. Fetal hearts were still present, approximately 170. No progress for the past two hours.

Under ether anesthesia a breech extraction was attempted with no success except a descent of the first child to the level of the sacrum. The presence of fetal intestines was noted in the vaginal canal and on examination the presence of Siamese twins was recognized and operative delivery was instituted.

Episiotomy, deep mediolateral, and destructive operation performed on the first twin by severing the anterior and posterior arms at the shoulder. Craniotomy performed through the roof of the mouth followed by severance of the thoracic attachment and delivery of the first twin. The arms were severed first. The second child was extracted with no difficulty. Both were stillborn, weighing 3 pounds 13 ounces and measuring 17.5 inches in length, and 4 pounds 3 ounces and 17 inches in length, respectively. Both were females.

During the above operative delivery the patient developed severe shock, which was controlled with 2,000 c.c. of glucose and later with 500 c.c. of blood.

Immediately following the birth of the twins the placenta was delivered manually and during this procedure the presence of the third fetus was ascertained and delivered by version and extraction. This was a living female child, weighing 4 pounds 15 ounces, followed by manual extraction of the second placenta. The third fetus was perfectly normal and was resuscitated with little difficulty, despite the fact of the long operative delivery and prolonged anesthesia.

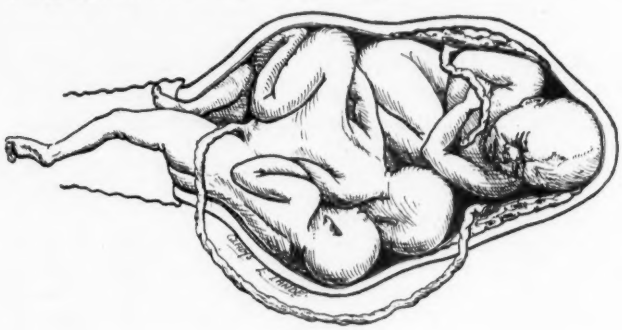

Fig. 1.

Immediate postpartum condition was poor. No effort was made to repair the cervix or perineum. The uterus and vagina were packed and the patient given ergotrate intravenously and ergometrine intramuscularly to control the excessive hemorrhage, and she was sent back to bed.

Patient received a second 500 c.c. blood transfusion on her first day of the puerperium and a third on her ninth day. The pack was removed in twenty-four hours. Ten grains of sulfanilamide were given, four doses daily, for four days. The inlying catheter which was introduced in the delivery room at the termination of the delivery was allowed to remain in the bladder for three days, due to the marked edema of the vulva and vaginal walls. One gallon hot saline douches were given daily.

Her puerperium was uneventful, highest temperature 101.4° F. Fever disappeared by gradual lysis and she was discharged from the hospital on her twenty-second postpartum day. Pelvis was negative on discharge, except for a granulating episiotomy and perineal laceration.

This patient subsequently received treatment in our out-patient gynecologic clinic and was readmitted to the hospital in April, 1940, for perineorrhaphy. The cervix having healed spontaneously, no operative therapy was deemed necessary.

Mother and child were in excellent condition on last visit to the out-patient department for postoperative check-up.

REFERENCE

(1) *Ilberg, George:* Ztschr. f. Geburtsh. u. Gynäk. **117:** 492, 1938; **119:** 369, 1939.

250 South Eighteenth Street

LEIOMYOMYXOSARCOMA OF THE UTERUS

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(From the Gynecological Service of the City Hospital)

THE case detailed below is reported because of the interesting clinical history, the comparatively rare pathologic entity (as evidenced by a review of the literature of the last twenty years), and the fact that this apparently highly malignant tumor was restricted as to its metastatic manifestations.

A 50-year-old, colored female was admitted to the Gynecological Service of City Hospital on May 3, 1940, with a chief complaint of pain and swelling of the abdomen of eighteen years' duration. The patient first noticed a painful mass in her abdomen eighteen years ago and went to another institution to seek treatment. There she was told that she had heart trouble and did not need an operation. From that date she had seen no physician until two months prior to admission. During this interval, the patient had only slight discomfort and constipation. The last menstrual period was two years ago with no bleeding since. A single gravidity resulted in a miscarriage. There was no further relevant history.

Physical examination revealed a chronically ill, colored female of about 50 years of age. The head and neck were essentially negative. The lungs showed slight dullness to percussion in the left lower chest anteriorly and posteriorly and occasional fine râles at both bases. Both diaphragms were raised. The heart was normal in size, the rate was regular but somewhat rapid, and no murmurs were heard. The abdomen was enlarged beyond that of a term pregnancy and filled with a hard irregular mass that extended from the pelvis to under the costal margin. The mass seemed to originate in the pelvis, was fixed, and not tender. There was no demonstrable free fluid. Above the umbilicus and just under the skin, a circumscribed solid mass about 15 cm. in diameter and relatively freely movable was palpated. Vaginal examination revealed normal external genitalia and perineum. No cervix could be palpated as it was apparently effaced. The whole pelvis was filled with the mass.

The laboratory data were as follows: Blood count: Hb, 9 Gm. (Sahli); red blood cells, 3.86 m.; white blood cells, 24,000; differential, 66 per cent segmented neutrophiles, 19 per cent stab forms, 15 per cent lymphocytes. Blood sedimentation time: 12 minutes. Urinalysis: negative. Blood Wassermann: negative.

Various diagnoses were made by the several members of the staff; mine was mammoth fibroids with sarcomatous degeneration. Due to the fact that the tumor could not be definitely demonstrated to be an inoperable malignancy, it was decided to do an exploratory laparotomy.

On May 8, 1940, under cyclopropane anesthesia, the abdomen was opened. A large solid mass was found which arose from the uterus. There were numerous smaller tumors, ranging in size from that of a pea to orange, which were attached to the peritoneum, the mesentery, and the omentum. Another very large mass was found in the upper abdomen. This tumor adhered firmly to the under surface of the diaphragm and liver. The uterine mass, which extended well above the umbilicus, was removed. During this procedure the patient went into shock and a transfusion was immediately started. Since the patient's condition was becoming increasingly grave, 2,000 c.c. of normal saline were placed in the abdomen, and it was immediately closed. In spite of the transfusion of 900 c.c. of blood, the patient failed to recover from the shock and died four and one-half hours later.

The following is a summary of the findings at autopsy and the pathologic report. On opening the abdomen it was found to be filled with a tremendous tumor which was round in shape and reached from the diaphragm to the pelvic brim. It was not attached to any organ but adhesions bound it to the serosal membranes of the peritoneal cavity, and it was removed with some difficulty. Section of the mass revealed a central cystlike cavity and many areas of necrosis and hemorrhage. There were whorls of pale whitish tissue which were solid and homogeneous in character. The parietal peritoneal surfaces were studded with small metastatic nodules. Larger nodules (1 to 3 cm. in diameter) were noted along the aorta. The heart, lungs, abdominal parenchymal and hollow organs,

and lymph nodes all failed to show on gross or microscopic examination any evidence of metastases. There were no pathologic changes in the heart suggestive of organic heart disease. The tumor was described microscopically as being formed of large and small areas of atypical smooth muscle cells which varied in size and shape. The nuclei were spindle, round, or polygonal in shape, hyperchromatic and revealed numerous atypical mitoses. Between the muscle bundles were many large and small areas of typical myxomatous change containing occasional stellate cells. Several smaller tumor masses of the uterus revealed on microscopic examination the typical changes of benign uterine myomas.

The pathologic diagnosis was: multiple myomas and multiple leiomyomyxosarcomas of the uterus with peritoneal sarcomatosis.

I wish to express my thanks to Drs. J. G. Sharnoff and Cyril Solomon from whose autopsy and pathologic reports the latter part of this paper freely quotes.

AN IMPROVED INSUFFLATION CANNULA

ROBERT S. MILLEN, M.D., AND ELWOOD JONES, M.D., WESTBURY, N. Y.

TUBAL insufflation and uterosalpingography recently was made easier and more accurate through the designing, by E. D. Colvin,[1] of a screw tip cannula, which, without pain, may be screwed into the external os of the cervix tightly enough to ensure against leakage, without need for tenaculum or traction on the cervix. We have incorporated into this cannula (*A*) a stylet cannula (*B*), similar to that of an old style insufflator, except that the end is closed and the openings are on the side (*C*), thus allowing a smaller tip, which will pass through the internal os easier and at the same time lessen danger of traumatizing tissue with the sharp open end. We feel that the stylet cannula reaching into the fundus acts as a guide for the screw cannula, obviating any false passage, and also insures that a tight internal os does not cause obstruction. In addition, it prevents obstruction due to acute angulation of the cervix on the body.

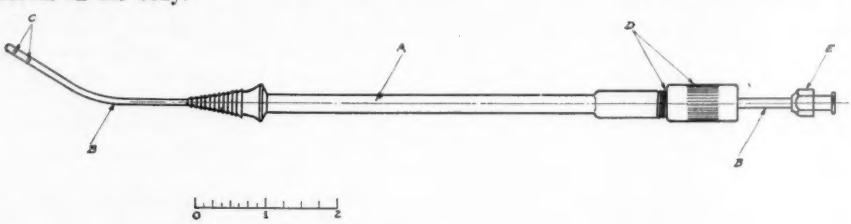

Fig. 1.

At the proximal end of the screw cannula is a lock joint (*D*) which works by screwing down, thus compressing a small section of rubber tubing as an expanding washer, and forming an airtight seal. At the proximal end of the instrument, which is, of course, the end of the inner cannula, a Luer Lok connection (*E*) is screwed on so that a syringe may be applied directly for salpingogram injections, or for a Luer Lok connection with an insufflation apparatus. This connecting piece may be unscrewed for replacing the small rubber ring in the compression valve.

In use, the uterine cannula is inserted into the uterus and, while being held with one hand, the outer screw cannula is slid forward and gradually screwed into the external os, until sufficiently snug to be airtight.

If traction is needed on the cervix to slide the inner cannula past the internal os, the screw cannula may be utilized for this purpose by screwing it into the cervix after the inner cannula has reached the internal os. The latter may then be passed into the fundus.

Finally, the lock joint is closed by turning it down in a clockwise direction. Insufflation or uterosalpingography may then be proceeded with as usual.

REFERENCE

(1) *Colvin, E. D.:* AM. J. OBST. & GYNEC. **37**: 168, 1939.

A HARD RUBBER PLAQUE FOR ANCHORING AND FACILITATING THE REMOVAL OF RADIUM APPLICATIONS TO THE BODY OF THE UTERUS

BROOKE M. ANSPACH, M.D., PHILADELPHIA, PA.

THERE are certain disadvantages in retaining radium with cervical and vaginal packing. It favors accumulations of blood or endometrial debris in the endometrial cavity and the possible passage of minute fragments into the tubes.

When the vaginal outlet is relaxed, the pack and the rubber tubes containing the radium may be displaced by an increase of intra-abdominal pressure from vomiting, coughing, or sitting up in bed.

As the bulk of the pack interferes with urination, catheterization often becomes a matter of necessity. One may use a retention catheter but fussy patients are annoyed; it may predispose to cystitis, and there is some pain during its removal.

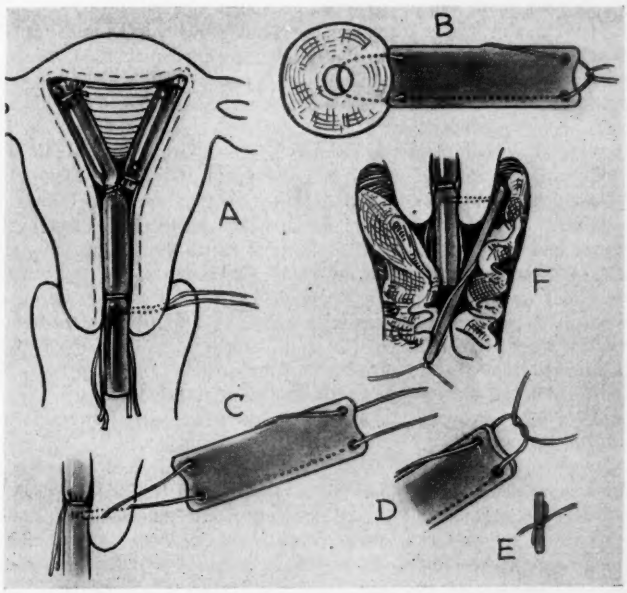

Fig. 1.—*A*, The radium in platinum capsules with walls 1.5 mm. thick is placed in black rubber tubes singly or in tandem. One to three capsules are used; the larger number is used in carcinoma of the fundus. The capsules are suitably disposed to cover as much of the uterine interior as desired. *B, C, D*, The anchoring thread is a fish-line passed first with a sharp needle through the wall of the cervix into the cervical canal, then with a thin round point needle through the rubber tubing in the midline below the radium, and finally with a sharp needle back to the vaginal surface of the cervix about a half inch from the point of introduction. *D, E*, The ends of the thread are carried through the perforations in the plaque and tied as indicated. *F*, The position of the plaque and the packing at the end of the procedure are shown.

To overcome these difficulties, for several years I have used with much satisfaction the hard rubber plaque herewith illustrated. It ensures free drainage from the uterus and does away with anything more than a few folds of gauze. The radium is securely held in place so that the patient may sit up or even get out of bed to empty the bladder.

Catheterization is avoided; the patient's local discomfort is reduced to a minimum. The anchoring thread is readily accessible at the vaginal outlet and removal of the radium is made easy.

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

IMMEDIATE PUERPERAL DEATH*

AN ANALYSIS OF 318 MATERNAL DEATHS OCCURRING WITHIN TWENTY-FOUR HOURS OF THE DELIVERY OF A VIABLE INFANT

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(From the Department of Obstetrics, Hahnemann Medical College)

THE formation of local committees on maternal welfare throughout the United States has resulted in the accumulation of much data on puerperal deaths. These data offer material which previously was not available for study. Among the facts noted is the time interval between fetal birth and maternal death. Maternal death within twenty-four hours of delivery of a child, at or beyond the twenty-eighth week of gestation, has been selected for this study. The material is analyzed to show the frequency, causes, preventability, and avoidable factors in such deaths.

The data were compiled from the records of the Committee on Maternal Welfare of the Philadelphia County Medical Society from 1931 to 1938, inclusive. This committee classified maternal deaths as:[1, 2] (1) true maternal deaths, in which pregnancy, labor, or the puerperium is directly responsible for the death, (2) deaths in which other diseases are the primary cause, but pregnancy, labor, or the puerperium is a contributory cause, and (3) those deaths in which pregnancy or labor had no effect (nonobstetric).

The true maternal deaths and those in which the obstetric condition was a contributing factor were analyzed by the committee to determine if the death was preventable or not preventable. If it was preventable, the avoidable factors were noted. The opinion of the majority of the committee was the final decision in the classification of the death, in assigning its preventability and in the noting of the avoidable factors.

Frequency.—During this eight-year period, 1,587 women who were pregnant or in whom the pregnancy was recently terminated died in Philadelphia. Excluding abortion and ectopic gestation, 937 (59 per cent) patients died after the pregnancy had advanced to or beyond the twenty-eighth week of gestation. Three hundred and eighteen pregnant women died within twenty-four hours of the delivery of a viable child. Consequently, in this study, a maternal death within twenty-four hours of the delivery of a viable child occurred once in every five maternal deaths due to all causes, and once in every three maternal deaths in which the pregnancy had advanced to, or beyond, twenty-eight weeks.

Causes of Death.—Of these 318 patients, 26 (8 per cent) (Table I) died from nonobstetric causes. The remaining 292 (92 per cent) (Table II) died with pregnancy or labor as the sole cause or a contributory factor in the death. This latter group of deaths are classified as obstetric deaths.

Of the 292 obstetric deaths, 262 (90 per cent) died solely as the result of obstetric causes; in the remaining 30 (10 per cent), pregnancy or labor was a contributory factor in the death. Of the 292 obstetric deaths, it was noted that the three most common causes of death, postpartum hemorrhage (19.5 per cent), shock (16.4 per cent), and eclampsia (11.6 per cent), accounted for 47 per cent of the deaths while the next three most common causes, placenta previa (9.2 per cent), placenta abruptio (9.2 per cent), and ruptured uterus (6.1 per cent) accounted for 24 per cent of these deaths.

*Read at a meeting of the Obstetrical Society of Philadelphia, May 2, 1940.

TABLE I. NONOBSTETRIC CAUSES OF DEATH

DISEASES	NUMBER
Total	26
Pneumonia (lobar and bronchopneumonia)	7
Valvular heart disease	4
Acute cardiac dilatation	3
Rheumatic and chronic endocarditis	3
Acute pulmonary edema	2
Miscellaneous, one each of the following: chronic rheumatic fever, acute yellow atrophy of liver, influenza, purpura hemorrhagica, epilepsy, cerebrospinal meningitis, acute toxemia	

TABLE II. OBSTETRIC CAUSES OF DEATH

DEATHS WITH PREGNANCY OR LABOR AS SOLE OR CONTRIBUTORY CAUSE	NO. 292	PER CENT 100.0
True maternal deaths (pregnancy or labor sole cause of death)	262	89.7
Diseases:		
Post-partum hemorrhage	57	19.5
Shock (obstetric, puerperal, etc.)	48	16.4
Eclampsia	34	11.6
Ruptured uterus	27	9.2
Placenta previa	27	9.2
Placenta abruptio	18	6.1
Pulmonary embolism	13	4.4
Toxemia	10	3.4
Inversion of uterus	8	2.7
Sepsis	7	2.3
Nephritis	6	2.0
Pre-eclampsia	4	1.3
Miscellaneous: One each of kidney of pregnancy, vomiting of pregnancy, puerperal sudden death	3	1.0
PREGNANCY OR LABOR CONTRIBUTORY TO DEATH	30	10.3
Diseases:		
Acute cardiac dilatation	5	1.7
Mitral stenosis	3	1.0
Lobar pneumonia	3	1.0
Cerebral embolism	3	1.0
Embolism	2	0.6
Myocarditis	2	0.6
Influenzal toxemia	2	0.6
Miscellaneous: One each of pyelitis, rheumatic endocarditis, thrombosis in broad ligament (spontaneous) acute myocardial failure, myocardial insufficiency, cerebrospinal meningitis, cesarean section, cardiac decompensation, spinal anesthesia, anesthesia	10	3.4

Preventability and Avoidable Factors.—In the opinion of the analysis committee, 121 (41 per cent) of the 292 obstetric deaths were unavoidable catastrophies. In the remaining 171 patients (59 per cent) of this group, an avoidable factor was judged causative of the death. In the records of the management of these patients, the committee found that ignorance or self-neglect of the patient was the avoidable factor in 39 (23 per cent), while in 132 (77 per cent) there was an error upon the part of the attending physician as the preventable factor. Of this latter group of 132 patients, the physician's prenatal care was inadequate in 10 per cent, and his judgment or/and technique in the management of their obstetric problem was deficient in 90 per cent.

Frequency of Twenty-Four-Hour Preventable Deaths Assignable to Physician.—One hundred thirty-two (14 per cent) of the 937 patients who died after the pregnancy had advanced to or beyond the twenty-eighth week of gestation were

twenty-four-hour deaths assignable to the physician's error. One hundred and thirty-two (40 per cent) of the 318 deaths that occurred within twenty-four hours of the delivery of a viable child were due to preventable errors upon the part of the attending physician.

COMMENT

Any improvement in maternal mortality rates comes through decreasing the preventable deaths. In this study the records indicate that the avoidable factors ascribed to the attending physician are frequently the result of his lack of knowledge and skill. It is not too much to ask the physician who accepts the responsibility of obstetric care to be fully acquainted with normal pregnancy, labor, and the puerperium. He should remember that a very large percentage of his patients will be normal. Familiarity with the normal will make recognition of the abnormal relatively easy. If he is unable to cope adequately with the abnormalities, he should seek expert advice and help. In this connection a factor rather frequently noted was the performance of difficult operations, notably version and extraction, by physicians inadequately trained in such procedures. Hospital surroundings make many men too bold and quick in their decision to terminate labor operatively. The records show that, in quite a few of these patients, operative work was performed when the time of election had not arrived, or had passed. Several patients had operative procedures performed after long trial labors without adequate preoperative rest and preparation. They were dehydrated, acidotic, and tired. Fatal shock frequently followed.

Many patients in this series did not have the type of prenatal care which brought them to their delivery in the best possible physical condition. Quite a few showed anemia, and many of the cardiac patients had insufficient rest periods in the latter months of pregnancy. Potential toxemia patients failed to have sufficient number of prenatal visits, and those who had actual toxemia had little or no observation. X-ray study of the pelvis was infrequently done in patients with cephalopelvic disproportion. X-ray pelvimetry is of great value in borderline cases, and is recommended before labor.

The number of deaths due to post-partum hemorrhage indicates that the third stage of labor calls for more careful management, particularly in regard to awaiting the complete separation of the placenta before attempts at expulsion are made. The manual removal of the placenta was occasionally incomplete. Quite a few patients died from post-partum hemorrhage because of poor contractile power of the uterus following operative delivery in cases of uterine inertia. Atony of the uterus should be suspected in all patients manifesting varying grades of inertia, and preparations made to combat it following the second stage of labor. Several patients died following the exhibition of large doses of pituitary substance which caused deep cervical lacerations or rupture of the uterus. Many of the patients dying of the various forms of ante-partum or post-partum hemorrhage did not receive the benefit of blood transfusions. This procedure was too little utilized, especially in the early years of the study. The larger hospitals' blood banks and the more general procurement of donors preoperatively have ameliorated this situation to a certain extent, and transfusion always should deserve prime consideration.

SUMMARY

1. Three hundred and eighteen (33 per cent) of 937 maternal deaths after the twenty-eighth week of gestation occurred within twenty-four hours of delivery.

2. Two hundred and ninety-two (92 per cent) of these 318 deaths were obstetric deaths.

3. Of the 292 obstetric deaths, 71 per cent were caused by postpartum hemorrhage, shock, eclampsia, placenta previa, placenta abruptio, and inversion of the uterus.

4. Of the 292 obstetric deaths, 171 (58 per cent) were judged preventable.

5. The preventability of these 171 obstetric deaths were assigned to the physician in 132 (77 per cent) and to the patient in 39 (23 per cent).

6. Since 12,000 women die from all puerperal causes in each year in this country, should a similar ratio of preventability obtain as occurred in this study, the elimination of the immediate puerperal preventable deaths from the standpoint of the physician's education or skill would save 1,000 lives annually.

I wish to acknowledge the help of the members of the Committee on Maternal Welfare of the Philadelphia County Medical Society in compiling the records, the aid given by Miss D. Malkiel in compiling the statistics, and the advice and suggestions given by Dr. Douglas P. Murphy and Philip F. Williams in the preparation of the manuscript.

REFERENCES

(1) Maternal Mortality in Philadelphia 1931-33, P. F. Williams, Philadelphia County Medical Society, 1934. (2) *Runnels, S. C.:* J. Am. Inst. Homeo. **25**: 1408, 1932.

250 South Eighteenth Street

Society Transactions

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF MAY 2, 1940

The following case reports and papers were presented:

A Case of Hematuria Complicated by Pregnancy. Dr. Owen J. Toland.

Ovarian Pregnancy, Primary or Secondary? Drs. Bernard Mann, D. R. Meranze, and Benjamin Leff. (For original article, see page 322.)

Immediate Puerperal Death. H. D. Lafferty. (For original article, see page 342.)

MEETING OF OCTOBER 3, 1940

The following papers were presented:

The Emergency Control of Post-partum Hemorrhage: Experience with a Supplementary Technique. Drs. C. C. Briscoe and R. A. Wilson.

Siamese Twins (Thoracopagic) Complicating Triplet Pregnancy. Drs. R. J. McNeil, H. L. Crowther, and N. F. Paxson. (For original article, see page 337.)

Some Cardiologic Factors of Importance in Obstetric Practice. Dr. W. G. Leaman, Jr.

ST. LOUIS GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 17, 1940

The following papers were presented:

Endocrine Factors in Gynecologic Disease. Dr. Willard M. Allen. (By invitation.)

Increased Uterine Response to Pituitrin Following Alkalinization. Dr. Roy V. Boedeker.

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 4, 1940

The following papers were presented:

A Review of 94 Mixed Mesodermal Tumors of the Uterus. Drs. Morris Glass and J. W. Goldsmith. (For original article, see page 309.)

The Toxemias of Pregnancy. Drs. Frank P. Light, D. S. Fettes and N. J. Mazzola.

Iontophoresis in the Treatment of Pelvic Infections. Drs. Charles A. Gordon and A. H. Rosenthal. (For original article, see page 237.)

Local Refrigeration in Genital Cancer. Drs. Charles A. Gordon and Joseph V. Cresci. (For original article, see page 281.)

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Labor

Spiller, Violet: Duration of Labour in Primiparae, Lancet 2: 733, 1939.

In 1,400 consecutive patients delivered by the vaginal route, all of whom received analgesics during labor, there was a low but definitely positive correlation between the age of the patient and the duration of labor. The average length of labor of patients between the ages of 18 and 39 was 23 hours and 39 minutes. Half of the patients had labors lasting less than 20 hours. In the age group between 24 and 27 years, which represented nearly two-fifths of the total patients, 65 per cent had a shorter than average labor, and half of the patients had labors lasting between 7 and 18 hours.

CARL P. HUBER.

Moir, Chassar: The Occipito-Posterior Positions of the Vertex and Their Complications, Brit. M. J. 2: 555, 1938.

A brief discussion of the causes, dangers, and diagnosis of this abnormality is offered. The chief cause of the difficulty is thought to be a maladjustment of the shape of the fetal head to the shape of the birth canal. Unusual postures of the fetus in utero, an increased inclination of the pelvis or a poorly flexed fetal head favor nonrotation. When nonrotation, or malrotation occurs in a large pelvis with a small head, or a deficient perineum, delivery is usually easy. Frequently a mild degree of pelvic contraction accompanies nonrotation. These cases are more difficult to manage.

Radiologic methods of study are new aids in diagnosis. Late engagement of the head, and early rupture of the membranes in the absence of disproportion between the head and the pelvis are signs of malposition. Fetal heart sounds heard in the flank, and peculiar uterine contractions are often present. Labor may be obstructed by an edematous scalp. Vaginal examination is essential and an anesthetic is required in any case of doubt before forceps delivery is undertaken.

The dangers to mother and fetus are grave in this condition. Fetal mortality is high and puerperal sepsis frequent.

F. L. ADAIR AND S. A. PEARL.

Vartan, C. Keith: Cause of Breech Presentation, Lancet 1: 595, 1940.

From a review of 969 breech deliveries, the author concludes that it is wrong to teach that the cause of the breech presentation at term is a pelvic anomaly which prevents the head from entering the pelvis. He believes that the cause is the failure of the fetus to undergo a spontaneous cephalic version. Spontaneous version was prevented by an extended attitude of the fetus in 37.3 per cent of the group studied, by the presence of another fetus in 23.6 per cent and by prematurity in 9 per cent. These three factors may account for 70 per cent of breech presentations. In 22.9 per cent of the cases no cause was recorded. Placenta previa was present in only 3.2 per cent and disproportion in only 1.3 per cent, and for that reason neither can be considered as an important etiologic factor. Pelvic tumors, and an abnormally shaped uterus, hydrocephalus, hydramnios, and anencephaly are so rare as to be of little significance in the production of breech presentation.

CARL P. HUBER.

Crosse, Mary V.: Management of the Frank-Breech Presentation, Brit. M. J. **2:** 113, 1939.

In a series of 100 cases the child mortality rate was considerably reduced by using simple methods with no risk to the mother. In the first place, all unnecessary interference was eliminated; and, second, a special effort was made to provide a skilled and sufficient staff of attendants for each breech delivery.

The management of the delivery is kept as simple as possible; there is no interference except fundal and suprapubic pressure, unless definite indications arise. A leg is pulled down only when there is definite delay during the second stage, as the complete breech is a better dilator than the half-breech. In no case was it found necessary to bring down a leg during the first stage of labor. Traction is not used, as this extends the arms and head. Hot towels are not employed, as they obstruct progress and make handling of the infant difficult. In no case has the child suffered from this omission. Forceps are used only when there is difficulty with the aftercoming head. They are, however, always boiled and ready for use in emergency. Episiotomy has been performed in most of the later cases of the series, especially in primiparas, as it reduces pressure on the infant's head and also eliminates risk of a third-degree tear. It is done while the breech is distending the vulva.

The risk of stillbirths in this series was 4 per cent and the risk of neonatal death, 5 per cent.

J. P. GREENHILL.

Goethals, Thomas R.: Management of Breech Delivery, Surg. Gynec. Obst. **70:** 620, 1940.

The occurrence of breech presentation as a problem in the management of labor at term may be handled in one of three ways. The obstetrician may convert the breech to a vertex by the maneuver of external version; he may deliver the infant as a breech through the pelvis; or he may elect to perform cesarean section.

From a study of 2,035 pelvic breech deliveries and 58 abdominal cesarean sections in the Boston Lying-in Hospital from 1888 to 1937 inclusive, the following conclusions have been drawn.

1. About 7 per cent of primigravidas with breech presentations at term should be delivered by section.

2. Roentgenographic mensuration of the fetal head in utero has a definite if limited value in helping to diagnose fetopelvic disproportion. The ideal method of making a comparison of the fetopelvic relationship in breech presentation has not yet been determined.

3. The statistics and experience derived in this study indicate that, if delivery through the pelvis is selected as the method of choice, the second stage of labor should be terminated by breech extraction under full surgical anesthesia before the birth of the umbilicus has occurred.

WILLIAM C. HENSKE.

Stampfel and Tscherne: The Radiological Diagnosis of Postmaturity in the Fetus, Ztschr. f. Geburtsh. u. Gynäk. **119:** 31, 1939.

The authors set out to determine the normal state of development of the human skeleton by the time of delivery of the term infant, i. e., just which of the usually employed primary and secondary centers of ossification are present when the infant is born previous to nine days after, but not before nine days in advance of the calculated date of confinement. They show two previously reported charts of development of the human skeleton, refer to several others, and point out the lack of uniformity in these.

The experience of the authors with x-rays of 90 term newborn infants, 45 males and 45 females, leads them to conclude that a term infant will always

possess a well-developed secondary center of ossification at the distal end of the femur and usually a smaller secondary center at the proximal epiphysis of the tibia, whereas the cuboid will present in only one-half. Two carpals, the capitatum and the hamatum, the coracoid center and the medial humeral epiphysis will be present in 12 per cent, 20 per cent, and 30 per cent of the cases. This corresponds very well to the chart for development of the human skeleton (to which the authors do not refer) as furnished by Paul C. Hodges, except that in the latter's experience the coracoid usually does not appear until the end of the sixth month of extrauterine life.

They compare these normal cases with 22 infants which were delivered at least fourteen days after the estimated date of confinement. Again the x-rays were obtained on the newborn infants and not upon fetuses in utero. Slightly greater advance in bone development is observed in the postmature group but this is usually in the direction of the presence of those centers of ossification which may be present at term, but are not as commonly observed as the distal epiphysis of the femur and the proximal epiphysis of the tibia. They believe that the size of centers of ossification which are normally present in a term infant is a more reliable criterion of postmaturity than the actual presence of certain other centers of ossification, a conclusion arrived at by members of the Children's Bureau of the United States Department of Labor, who are in the process of tabulating the results obtained by x-rays of more than 1,200 newborn infants from various gestational periods and in different races.

This criterion of postmaturity is not practical for antenatal use and is only relatively sound. The authors do not state the incidence of visualization of the knee joint in utero, but show three reproductions of x-rays which do not prove routinely good intrauterine visualization of the fetal knee joint. It has certainly not been the experience in this country that a high degree of visualization in utero is possible even with special positioning of the patient. But if this were possible, the average error, which is in the neighborhood of 2.0 mm. with our most accurate roentgen methods, would void, for diagnostic purposes, such differences as the authors deal with when a bone diameter measures 5.0 mm. at term and 7.0 mm. in the postmature.

Finally, the authors have not taken into account the racial differences which do exert a definite influence upon bone development in the human being. They show in one of their tables that the female infant is farther advanced in bone development than a male infant of comparable gestational age. X-rays from the Children's Bureau series show a similar advancement in bone age of the negro infant over the comparable white infant. Interestingly enough, the degree of advancement in bone development of the female infant over the male, and of the negro infant over the white, is essentially the same as the authors have found in the postmature over the term infant. Racial differences might well account for the discrepancies which the authors point out in the previously reported charts of skeletal development.

A. L. DIPPEL.

Maizels, Gerald: High Puncture of the Membranes; A Review of 842 Inductions of Labour With the Drew Smythe Catheter, J. Obst. & Gynaec. Brit. Emp. 47: 237, 1940.

The author reviews his experience in 842 inductions of labor with the Drew Smythe catheter which enables one to do a high rupture of the membranes, allowing the escape of from one-half to one pint of liquor amnii. With this method one can leave the bag of forewaters intact, thereby lessening the dangers of ascending infection, prolapse of the umbilical cord and dry labor. The method, in general, is that devised by Hopkins (1814).

It was found that if surgical induction is preceded by a routine medical induction a better response is obtained. The patient is allowed to walk about after the rupture of membranes and if labor has not started by the third day the medical induction procedure is repeated, and if that does not succeed a

second puncture should be performed on the fourth day when the amount of liquor amnii withdrawn will usually be 6 to 8 ounces.

After high rupture of the membranes, labor begins at various intervals, but 86 per cent of the cases are in labor within four days. This method is considered unsuitable for breech presentation, but the safest for the treatment of disproportion.

The author feels that the results obtained indicate that maternal and fetal mortality rates are not increased, and the maternal morbidity and sepsis are lower than in any other surgical method of induction. The incidence of prolapse of the umbilical cord is not increased.

WILLIAM BERMAN.

Kreis, J.: The Justification of Rupturing the Membranes and Its Relation to Dilatation of the Cervix, Acta obst. et gynéc. Scandinav. **19**: 52, 1939.

In the opinion of Kreis, effacement and dilatation of the cervix are neuromuscular phenomena accompanied by physiologic or pathologic inhibitions arising in the cervix. The integrity of the bag of waters is either unnecessary or even an obstacle to the functional coordination of the uterine musculature. Premature or early rupture of the membranes with normal progress of labor constitutes a natural correction of an inhibitory disturbance. In unfavorable cases there is unsatisfactory development of the lower uterine segment and rupture of the membranes alone cannot overcome this. Since it is impossible to foretell at the beginning of labor with or without rupture of the bag of waters when disturbances in the lower uterine segment will arise, the author advocates the use of antispasmodics routinely before or after rupture of the bag of waters, regardless of whether this takes place spontaneously or artificially.

J. P. GREENHILL.

Cattaneo, Piero: Clinical Observations on the Treatment of Uterine Inertia, Associated with Premature Rupture of the Membranes, with Quinine-Calcium, Rassegna d'ostet. e ginec. (Naples) **48**: 257, 1939.

The author observed the progress of labor in 23 patients who had uterine inertia with early rupture of the membranes. The inertia was treated with intravenous injections of quinine-calcium. The average duration of labor after use of the drug was eight and one-half hours.

The uterine contractions proceed with normal force in some cases of premature ruture of the membranes but in other cases it may be necessary to hasten the labor to save the child. He reviews the literature, German and Italian, and observes that the maternal mortality rate is increased in cases with premature rupture of the membranes. For this reason the author felt justified to use quinine-calcium to effect earlier delivery.

His series of 23 cases includes 10 primiparas and 13 multiparas. All the mothers lived. Two infants were born dead, one of them a monster and the other a macerated syphilitic infant. Forceps were used in 12 cases. The membranes had ruptured prematurely more than twenty-four hours in 11 cases.

The dosage of the drug was: 5 c.cm., intravenously, in 16 cases; 2.5 c.cm. in a case dilated 8 cm. when inertia developed; and 6 to 15 c.cm. in divided doses, intravenously and intramuscularly, in 4 other cases.

CLAIR E. FOLSOME.

Heyrowski, K.: Dosage of Quinine in Labor, Deutsche med. Wchnschr. **66**: 576, 1940.

Citing a case of quinine intoxication in which a Werlhof type of purpura appeared, Heyrowski concludes that optimal doses of quinine for the initiation of labor lie in the range of 0.002 Gm. per kilo of body weight. The drug should not be given in excess of 0.1 Gm. per dose and not more than 3 or 4

doses. There is a great individual variation in uterine response to quinine and the amount required to sensitize the uterus to normal contraction impulses is small.

R. J. WEISSMAN.

Sibayama, K., Ogura, S., and Miyata, D.: Fetal Death Due to Quinine, Sankato Huzinka 5: 1, 1937.

At the Japanese Red Cross Lying-in Hospital, the authors observed three fetal deaths in a series of 802 cases where labor was induced by means of quinine. In one case the mother had received 0.6 Gm. (9 gr.) quinine, the second mother had been given 0.9 Gm. (13 gr.) and the third mother 1.5 Gm. (22½ gr.) by mouth and 1.5 Gm. by injection within forty-eight hours.

J. P. GREENHILL.

Blomfield, George W.: Administration of Pituitary Extract in the Third Stage of Labor, Brit. M. J. 2: 1083, 1938.

Experiments performed by the writer are claimed to show: (a) that there is no danger whatever in giving 1 c.cm. of pituitrin or pitocin during the third stage of labor; (b) that the amount of hemorrhage is not much affected: in the series there was a tendency to a smaller post-partum loss in the pituitrin cases.

It is not claimed that posterior pituitary extract should be given in the third stage as a routine treatment for all cases, nor should control of the fundus or the very watchful care that is necessary at this stage be relaxed, or be replaced by an oxytocic drug.

J. P. GREENHILL.

Emmrich, J. P.: The Prophylactic Intravenous Injection of Posterior Lobe Extract in the Period after Confinement, München. med. Wchnschr. 86: 329, 1939.

A study of statistics presented by various observers shows that the number of men who favor the injection is just as large as the number opposed to it, that the effect of the injections cannot be explained entirely by statistics and that even in a large amount of material there are sure to be discrepancies caused by differences in the biologic processes.

Used as a prophylactic, the intravenous injection of posterior pituitary lobe extract as a routine after confinement offers no advantages. Atonies, Credé manipulations, and manual removals occur almost as often as in women who have not had the injection. The differences are very small and lie within the limits of statistical errors.

On the other hand, it is advisable to use the prophylactic injection in selected cases of spontaneous deliveries, in which, as in hydramnios and twins, atonic hemorrhages can be expected as well as in most operative deliveries, especially in those with an insufficiency of labor pains. In these cases a physiologic course of the third stage of labor cannot be expected.

Therapeutically, in atonic hemorrhages this intravenous injection is the treatment of choice, and if used, it should be followed by an intramuscular injection after the delivery of the placenta. The effect of the intravenous injection is limited in duration and a definite relaxation may follow, and this is the reason why it has not come up to expectations.

C. E. PROSHEK.

Corbet, Robert M.: Post-partum Haemorrhage, With Special Reference to Partial Detachment of the Placenta, Brit. M. J. 2: 438, 1939.

The paper deals with the mechanism of separation of the placenta, suggesting that the Schultze mode, rather than that of Duncan, is the normal one.

Post-partum hemorrhage is divided into 3 classes: (1) Placental site hemorrhage; (2) true atonic hemorrhage, where there is no bleeding until after delivery of the placenta; (3) traumatic hemorrhage, where the bleeding comes from lacerations in some part of the birth canal.

Placental site hemorrhage is said to be caused by failure of the normal mechanism of placental separation, resulting in detachment of part of the placental margin before the central area has separated, with consequent escape of the retroplacental hematoma and loss of its important wedge action. Along the line where partial detachment has occurred, the maternal vessels are held open and continue to bleed, full retraction of the uterine muscle being prevented by the portion of the placenta still attached. There are various causes for this condition such as twins, hydramnios, fibroids, low implantation of the placenta, short cord, ill advised handling of the uterus, and attempts at expressing the placenta before it has entirely separated, morbidly adherent placenta, and prolonged operative deliveries. Some occur without apparent cause. In treatment, where hemorrhage has ceased, supportive measures are indicated before attempting delivery of the placenta, but when bleeding still continues, delivery should be accomplished promptly. The author discusses the Credé method and the manual removal of the placenta, methods of arresting hemorrhage after it has been removed, and the use of the oxytocic drugs in this connection. True atonic hemorrhage and traumatic hemorrhage are dealt with briefly.

FRED L. ADAIR, AND JOHN NEWDORP.

Smith, Clement A.: The Effect of Obstetrical Anesthesia Upon the Oxygenation of Maternal and Fetal Blood With Particular Reference to Cyclopropane, Surg. Gynec. Obst. **69:** 584, 1939.

Determinations were made of the oxygen content of arterial and venous blood from women during labor. Similar determinations were made upon the arterial and venous bloods of 3 groups of mothers and their infants at the moment of birth. These 3 groups represented routine deliveries under ether, under nitrous oxide-oxygen, and under cyclopropane anesthesia. In the second and third groups, the amounts of nitrous oxide and of cyclopropane were also quantitatively determined in the maternal and fetal bloods. An attempt was made to correlate the degree of oxygenation of maternal and fetal blood with the type of anesthetic used, and to discover the relationship between fetal anoxemia and the presence or absence of apnea in the newborn infant. The following observations seem significant:

Oxygenation of maternal blood during labor but before delivery an anesthesia was comparable to that observed by other authors for maternal blood at delivery without anesthesia. The arterial blood during labor showed a slight anoxemia.

In general, ether anesthesia produced a definite elevation of the maternal oxygen capacity, and of the oxygenation of maternal venous blood. Under the anesthesia the fetal oxygenation appeared to be satisfactory.

Nitrous oxide, administered with at least 20 per cent oxygen, produced a definite maternal and fetal anoxemia.

Under cyclopropane, the maternal blood showed a pronounced elevation of oxygenation in both the arterial and venous specimens. This is probably not due to the high concentration of oxygen administered with cyclopropane. The blood of infants delivered under this agent was somewhat better oxygenated than those born under nitrous oxide-oxygen. It contained less oxygen than the blood of infants delivered under ether, or that reported in the literature for those delivered without maternal anesthesia.

Pronounced anoxemia in the fetal blood at birth was not constantly accompanied by apnea of the newborn infant, except in babies delivered under nitrous oxide-oxygen. Fetal anoxemia is probably one of several factors which may operate to produce apnea. A surprising degree of fetal anoxemia may be associated with a normal onset of respiration.

Cyclopropane was present in the fetal blood in almost as high concentration as in the maternal blood. However, only about half as much nitrous oxide was found in the fetal as in the maternal blood.

Judged by biochemic data, cyclopropane as an obstetric anesthetic would appear to be perhaps less safe for the infant than the clinical appearance of the mother would indicate.

WILLIAM C. HENSKE.

Smith, Clement A.: Effect of Nitrous Oxide Oxygen Ether Anesthesia Upon Oxygenation of Maternal and Fetal Blood at Delivery, Surg. Gynec. Obst. 70: 787, 1940.

Judging by the amount of oxygen reaching the fetus at birth, the data presented indicate nitrous oxide and oxygen alone or combined with ether to be a less satisfactory obstetric anesthesia than ether alone.

WILLIAM C. HENSKE.

Kühnel, P.: The Treatment of Uterine Atony in Labor by Means of the Scalp Forceps, Acta. obst. et gynéc. Scandinav. 18: 466, 1938.

In 14 cases of pronounced uterine atony in which there was a cephalic presentation, the author used a scalp forceps with a weight attached to it. Other methods of stimulating labor pains were tried before this measure was employed. The results were so encouraging that the author recommends this precedure in cases of uterine atony where other measures have failed and the only alternative seems to be a craniotomy. The author also employed weight traction on a scalp forceps in a case of breech presentation.

J. P. GREENHILL.

Rucker, M. Pierce: Kielland Forceps, Virginia M. Monthly 66: 676, 1939.

The author states that the Kielland forceps exert practically no pressure on the baby's head when properly applied. The head can flex and extend and rotate as the birth canal may determine. For this reason delivery can be effected with less force than with any other type of forceps. Rucker on several occasions has been unable to deliver the baby with the axis traction forceps without using unwarranted force, and then, substituting the Kielland forceps, delivered the baby with ease. The classical conditions for forceps applications must be present with the Kielland forceps just as with any other model. To use the Kielland forceps successfully they must be applied according to the technique outlined by Kielland, which emphasizes accurate diagnosis of the position. Because of the ease with which these forceps are applied and the delivery effected, the author states that their chief fault is that one is tempted to use them when indications for forceps application are not present.

EUGENE S. AUER.

Daels and de Backer: Prophylactic Symphysiotomy, Zentralbl f. Gynäk. 63: 1119, 1939.

The writers advocate prophylactic symphysiotomy. They believe that in certain cases of cephalopelvic disproportion symphysiotomy should be carried out before labor begins when the patient is in good condition and not exhausted as after a hard labor. Such a procedure is without danger and a minor operation. The authors warn against abduction of the thighs in cases of prophylactic symphysiotomy because all they want to accomplish is to increase the diameter of the pelvis only ½ to 1 cm. so the pelvis may yield a little during labor.

J. P. GREENHILL.

Lundgren, A. T., and Boice, William A.: Knotting of Umbilical Cord, Illinois M. J. **76:** 451, 1939.

The authors report three instances of true knotting of the umbilical cord, resulting in the birth of stillborn fetuses. They estimate the incidence of this anomaly as about 0.3 per cent. The article quotes the views of various other writers on the etiology, mechanism, and effects of knots of the cord. It concludes with a complete bibliography of the subject as found in both American and European literature.

EUGENE S. AUER.

Dippel, A. Louis: Hematomas of the Umbilical Cord, Surg. Gynec. Obst. **70:** 51, 1940.

Hematoma of the umbilical cord, excluding its origin from rupture of a large varix or aneurysm of the umbilical vein, is an exceedingly rare complication of pregnancy and labor, occurring about once in 5,500 deliveries at or near term. The great majority of hematomas occur at approximately full term. Essentially one-half of all fetuses whose umbilical cords contain hemorrhagic areas are stillborn. The hemorrhage usually arises from rupture of the wall of the umbilical vein, though occasionally the wall of an umbilical artery ruptures; and rarely does the hemorrhage arise from the capillaries of the fetal end of the funis. The size of the hematomas varies greatly and the majority are located nearer the fetus than the placenta. Maternal complications of pregnancy are neither common nor limited to syphilis and the toxemias. The causes of rupture of an umbilical vessel are obscure and probably several factors enter into the development of a hematoma in each case. Before delivery, the only clinical evidence of the presence of a hematoma of the cord is that of fetal distress or occasionally that of vaginal bleeding.

WILLIAM C. HENSKE.

Friedlander, D.: A Case of Intrapartum Death Due to Intrauterine Rupture of the Umbilical Vein, J. Obst. & Gynaec. Brit. Emp. **47:** 334, 1940.

The author reports a case of intrauterine death of a fetus in a primipara in whom labor was induced. The cause of the fetal death was due to a rupture of the umbilical vein in utero. The mother's prenatal course had been entirely uneventful, and her serology was negative. She developed some intrauterine infection post partum, and the author suggests that this infection may have been the etiologic factor in the rupture of this vessel.

WILLIAM BERMAN.

Item

American Board of Obstetrics and Gynecology

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted at Cleveland, Ohio, by the entire Board from Wednesday, May 28, to Monday, June 2, 1941, inclusive, prior to the opening of the annual meeting of the American Medical Association in Cleveland.

Application for admission to Group A, Part II, examinations must be on file in the Secretary's Office not later than March 1, 1941.

Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates.

Candidates for *reexamination* in Part II must make written application to the Secretary's Office before April 15, 1941.

In accordance with the previously announced plans of the Board, the examinations to be given for the Board's fiscal year 1941-42 (ending with the Part II examination in June, 1942) will be the last for candidates under Group A and B classifications. Applications must be in the Secretary's Office at least 90 days in advance of the announced examination dates, which dates are published in the various medical journals. Following the close of the final date for receipt of Group B applications (October, 1941) and Group A applications (March, 1942) all candidates will be considered in one classification by the Board, thus doing away with the junior and senior groups for examination, and all candidates will be required to take the Part I examination (written paper and submission of case histories) as well as the Part II examination (oral and pathology).

Military service will not affect the eligibility of any candidate so far as the Board requirements regarding limitation of practice are concerned. Military service will under no circumstances be considered as an infringement of any regulations outlined in this Board's booklet.

The Board requests that all prospective candidates who plan to submit applications in the near future request and use the new application form which has this year been inaugurated by the Board. The Secretary will be glad to furnish these forms upon request, together with information regarding Board requirements. Address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

This Board will hold its annual dinner for Diplomates, and others interested in the work of the Board, on Wednesday evening, June 4, 1941, at the Wade Park Manor Hotel, Cleveland, Ohio, immediately following the close of the Part II examinations, which will be conducted in Cleveland in the spring, immediately prior to the opening of the annual A. M. A. meeting.